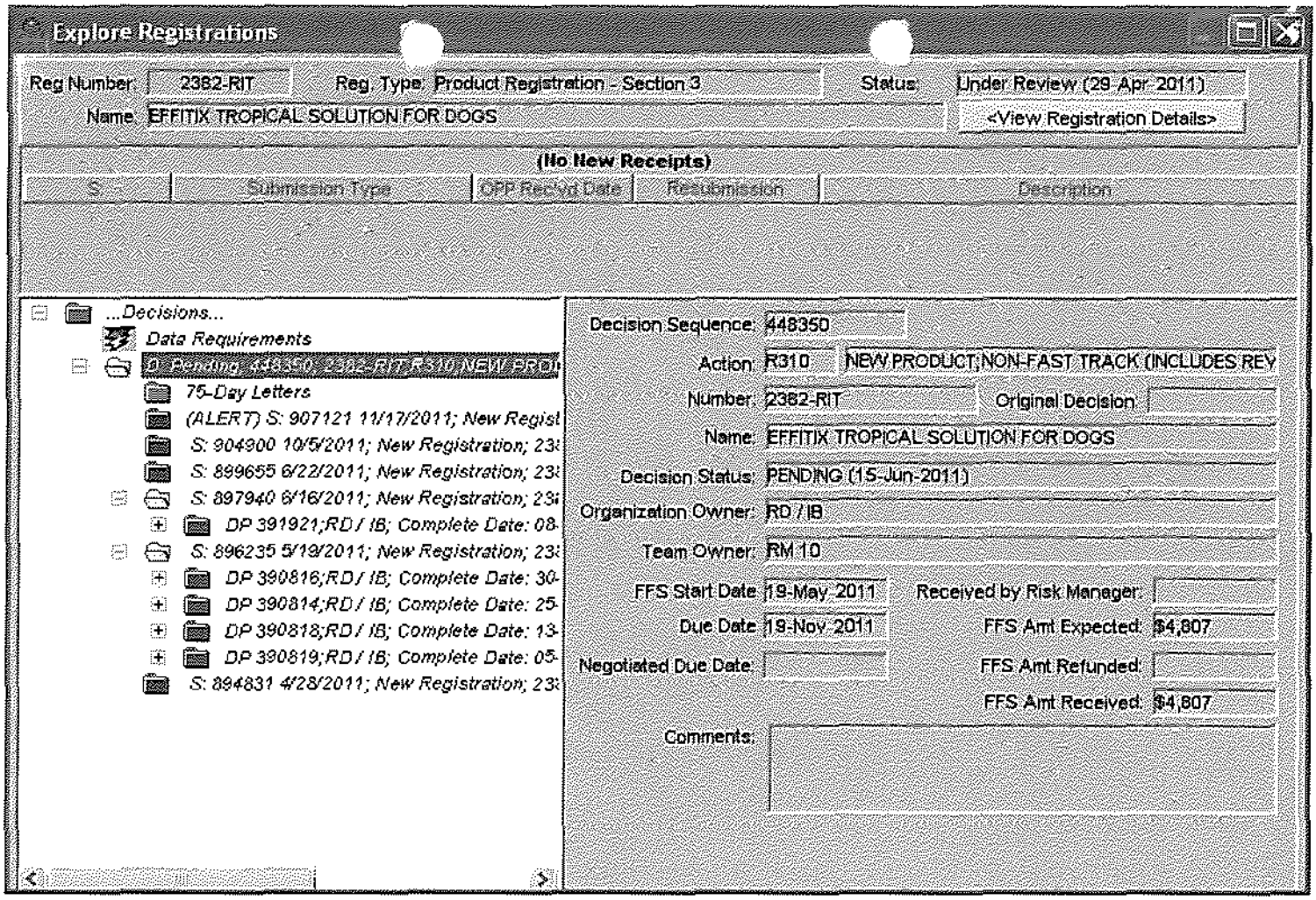
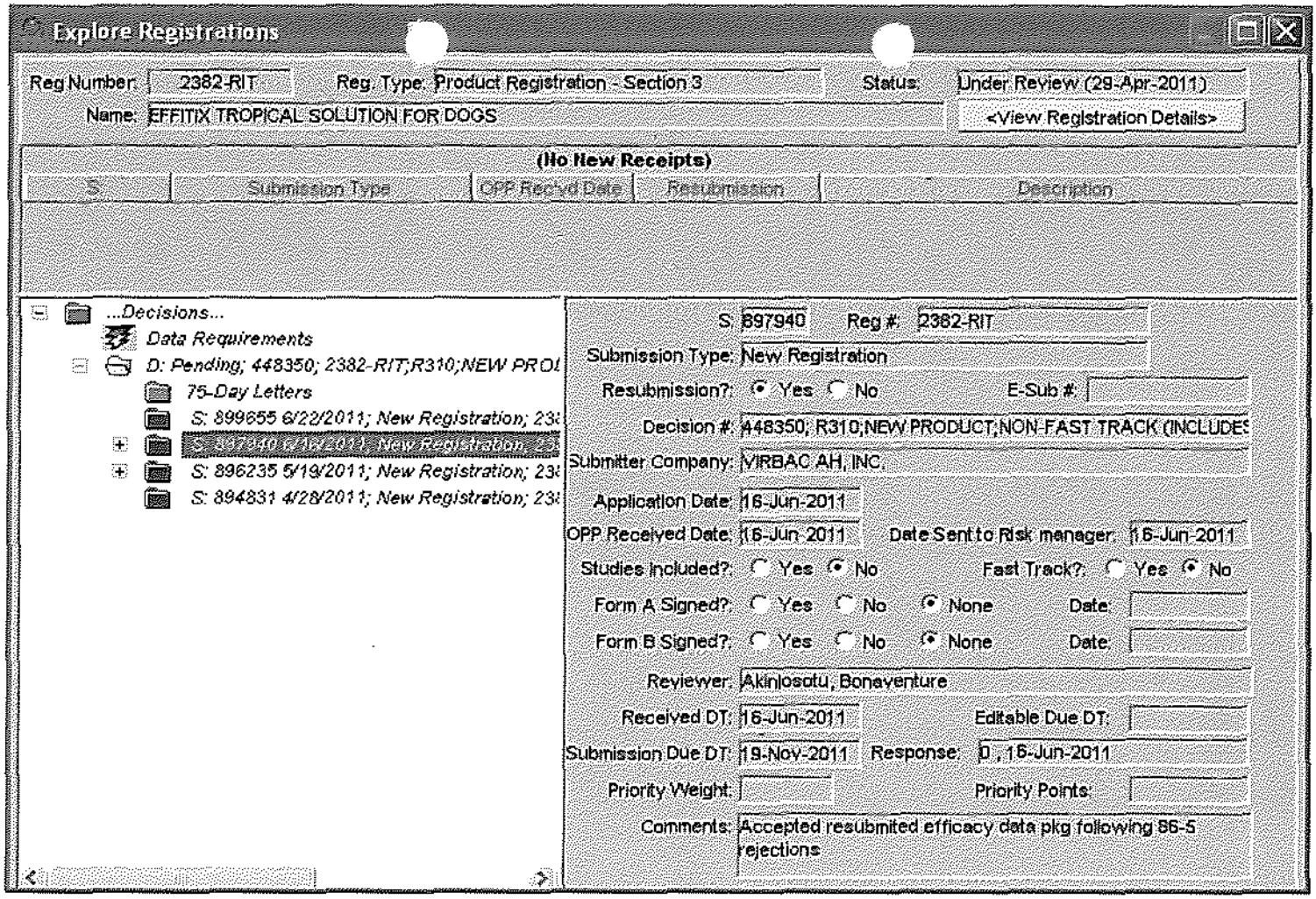
EPA Reg. No. 2382-187


Explore Registrations
Reg Number: 2382-RIT
Reg Type: Product Registration - Section 3
Status: Under Review (29-Apr-2011)
Name: EFFITIX TROPICAL SOLUTION FOR DOGS
<View Registration Details>
(No New Receipts)
S
Submission Type
OPP Recvd Date
Resubmission
Description
...Decisions...
Data Requirements
0: Pending; 448350; 2382-RIT; R310; NEW PRODU
75-Day Letters
(ALERT) S: 907121 11/17/2011; New Regist
S: 904900 10/5/2011; New Registration; 23
S: 899655 6/22/2011; New Registration; 23
S: 897940 6/16/2011; New Registration; 23
DP 391921;RD / IB; Complete Date: 08-
S: 896235 5/19/2011; New Registration; 23
DP 390816;RD / IB; Complete Date: 30-
DP 390814;RD / IB; Complete Date: 25-
DP 390818;RD / IB; Complete Date: 13-
DP 390819;RD / IB; Complete Date: 05-
S: 894831 4/28/2011; New Registration; 23
Decision Sequence: 448350
Action: R310
NEW PRODUCT;NON-FAST TRACK (INCLUDES REV
Number: 2382-RIT
Original Decision:
Name: EFFITIX TROPICAL SOLUTION FOR DOGS
Decision Status: PENDING (15-Jun-2011)
Organization Owner: RD / IB
Team Owner: RM 10
FFS Start Date: 19-May-2011
Received by Risk Manager:
Due Date: 19-Nov-2011
FFS Amt Expected: $4,807
Negotiated Due Date:
FFS Amt Refunded:
FFS Amt Received: $4,807
Comments:


Explore Registrations
Reg Number: 2382-RIT
Reg. Type: Product Registration - Section 3
Status: Under Review (29-Apr-2011)
Name: EFFITIX TROPICAL SOLUTION FOR DOGS
<View Registration Details>
(No New Receipts)
S
Submission Type
OPP Recvd Date
Resubmission
Description
...Decisions...
Data Requirements
D: Pending; 448350; 2382-RIT;R310;NEW PROI
75-Day Letters
S: 899655 6/22/2011; New Registration; 23
S: 897940 6/16/2011; New Registration; 23
S: 896235 5/19/2011; New Registration; 23
S: 894831 4/28/2011; New Registration; 23
S: 897940 Reg #: 2382-RIT
Submission Type: New Registration
Resubmission?: Yes No E-Sub #:
Decision #: 448350; R310;NEW PRODUCT;NON-FAST TRACK (INCLUDES
Submitter Company: VIRBAC AH, INC.
Application Date: 16-Jun-2011
OPP Received Date: 16-Jun-2011 Date Sent to Risk manager: 16-Jun-2011
Studies Included?: Yes No Fast Track?: Yes No
Form A Signed?: Yes No None Date:
Form B Signed?: Yes No None Date:
Reviewer: Akinlosotu, Bonaventure
Received DT: 16-Jun-2011 Editable Due DT:
Submission Due DT: 19-Nov-2011 Response: D , 16-Jun-2011
Priority Weight: Priority Points:
Comments: Accepted resubmited efficacy data pkg following 86-5 rejections

Efficacy

Explore Registrations

Reg Number: 2382-RIT Reg. Type: Product Registration - Section 3 Status: Under Review (29-Apr-2011)

Name: EFFITIX TROPICAL SOLUTION FOR DOGS <View Registration Details>

(New Receipts)

S	Submission Type	OPP Rec'vd Date	Resubmission	Description
896235	New Registration	19-May-2011	Yes / No	resubmission following 86-5 rejection

...Decisions...
- Data Requirements
- D: Pending; 448350; 2382-RIT;R310;NEW PROI
  - 75-Day Letters
  - S: 894831 4-28-2011 New Registration; 2

Rejected

S: 894831 Reg #: 2382-RIT

Submission Type: New Registration

Resubmission?: Yes / No

Decision #: 448350; R310;NEW PRODUCT;NON-FAST TRACK (INCLUDES

Submitter Company: VIRBAC AH, INC.

Application Date: 28-Apr-2011

OPP Received Date: 28-Apr-2011 Date Sent to Risk manager: 29-Apr-2011

Studies Included?: Yes / No Fast Track?: Yes / No

Form A Signed?: Yes / No / None Date:

Form B Signed?: Yes / No / None Date:

Reviewer: Akinlosotu, Bonaventure

Received DT: Editable Due DT:

Submission Due DT: 19-Nov-2011 Response: D , 28-Apr-2011

Priority Weight: Priority Points:

Comments: Application for registration

5/26/2011:-

- Make copies for routing to
- Chem ? Unreg tech ✓ Sent to regr
- Tox / PL – OK w/comments (unacceptable dermal sensiti) accept w/comments See (Rebuttal from Jim) / Copy sent to registrant
- Tox / CAS ✓ Sent to regr
- Tox / CRP ✓ okay w/comments (See pg 2) ✓ okay 7/18/11 / ✓ Copy sent to registrant
- Efficacy – 1 rejected Study 6/15/11 / Call Jim Barron = 919.228.6479

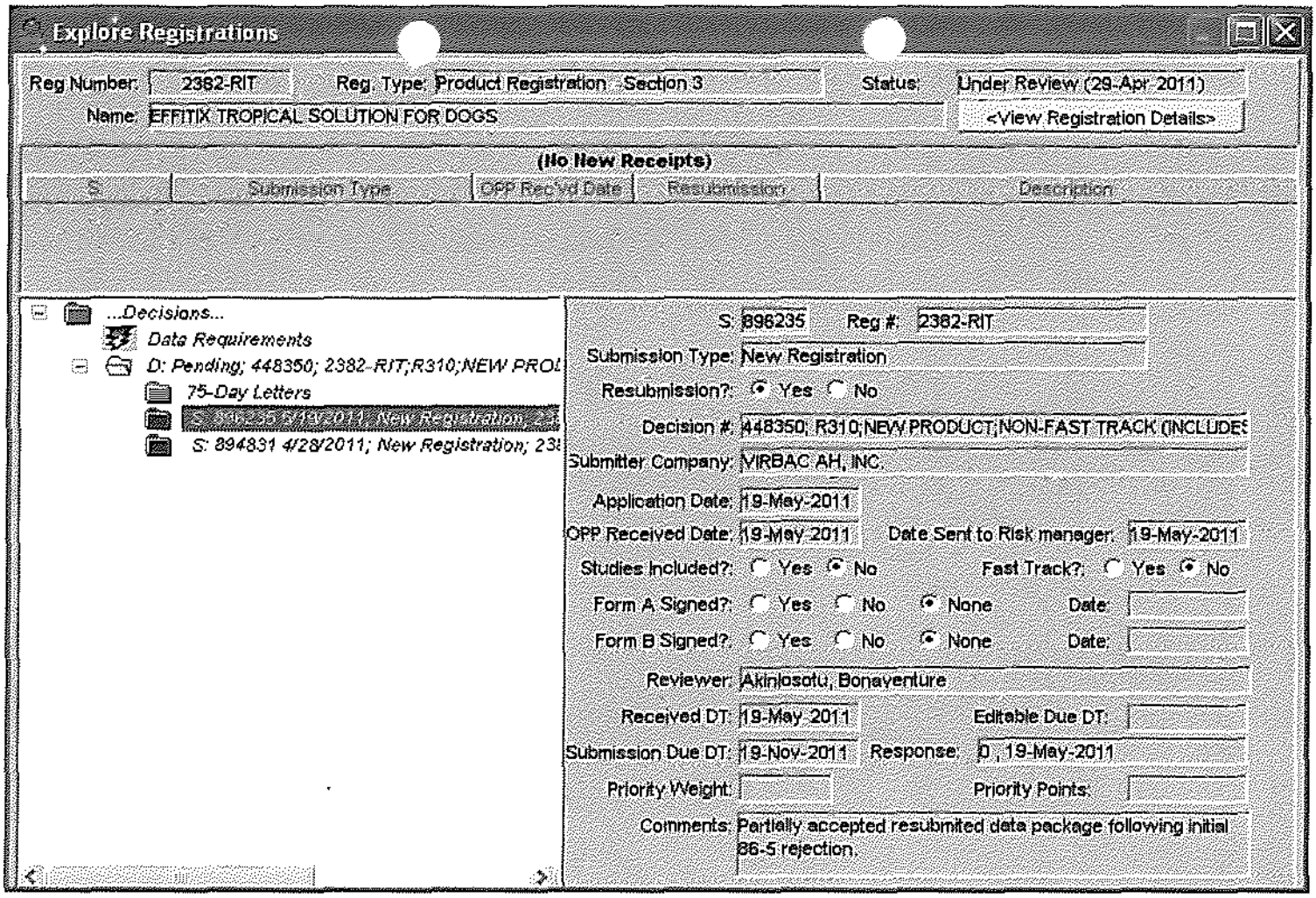
Cell: 919 534. 6018

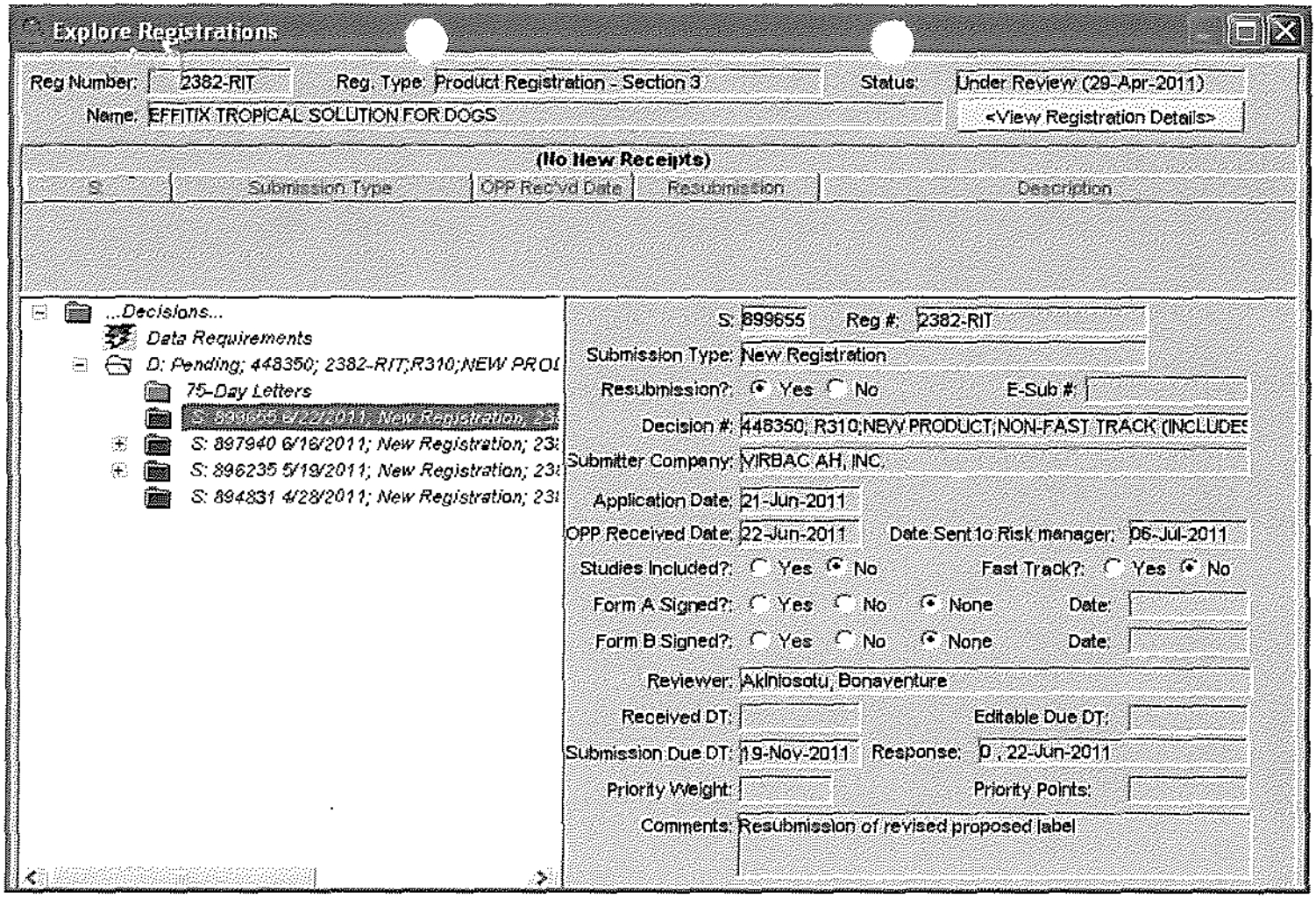
N/B:-

Data Def – Grps A & B Prod Chem) for Unregistered fipronil Tech ? See Richard
– 5 batch Analysis

7/8/2011:- Update, still waiting for "transmitted doc" of resubmission following 86-5 rejection

✓ okay 7/15/2011

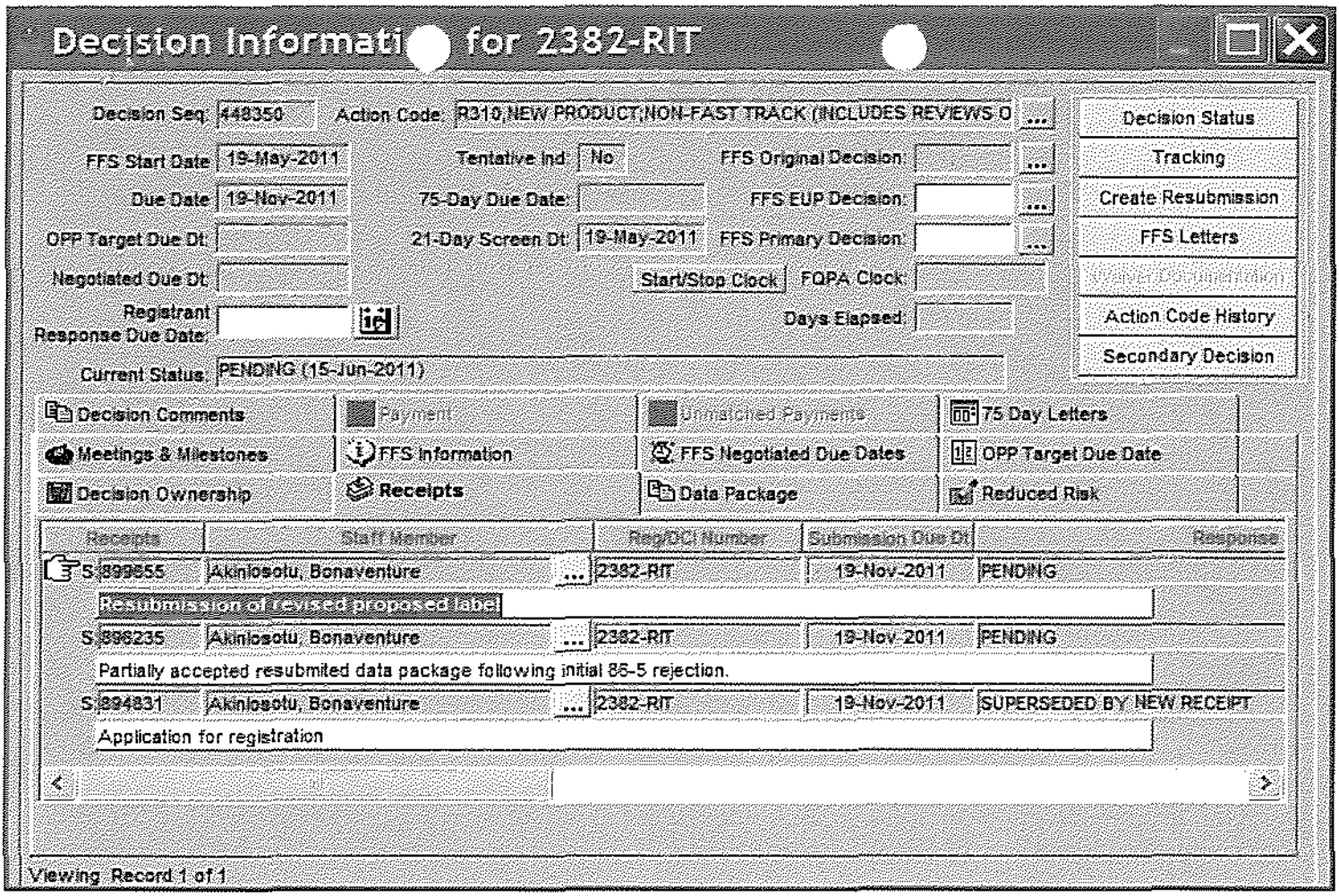

Explore Registrations
Reg Number: 2382-RIT
Reg. Type: Product Registration - Section 3
Status: Under Review (29-Apr-2011)
Name: EFFITIX TROPICAL SOLUTION FOR DOGS
<View Registration Details>
(No New Receipts)
S
Submission Type
OPP Recvd Date
Resubmission
Description
...Decisions...
Data Requirements
D: Pending; 448350; 2382-RIT;R310;NEW PROI
75-Day Letters
S: 894831 4/28/2011; New Registration; 23
S: 896235
Reg #: 2382-RIT
Submission Type: New Registration
Resubmission?: Yes No
Decision #: 448350; R310;NEW PRODUCT;NON-FAST TRACK (INCLUDES
Submitter Company: VIRBAC AH, INC.
Application Date: 19-May-2011
OPP Received Date: 19-May-2011
Date Sent to Risk manager: 19-May-2011
Studies Included?: Yes No
Fast Track?: Yes No
Form A Signed?: Yes No None
Date:
Form B Signed?: Yes No None
Date:
Reviewer: Akinlosotu, Bonaventure
Received DT: 19-May-2011
Editable Due DT:
Submission Due DT: 19-Nov-2011
Response: D , 19-May-2011
Priority Weight:
Priority Points:
Comments: Partially accepted resubmited data package following initial 86-5 rejection.



N/B:— Revised Proposed label ("minor errors detected & corrected by registr + some other word desf)

— Ask registrant (Dr. Craig Parks: 817/831-5030 to send "marked copy" of label ⇒ to show the revisions made

— Label stamped pin punched 6/22 replaced those of 4/28/11



Received 7/19/2011 BA

Decision #: 448350
DP #: (390814)
PRIA
Parent DP #:
Submission #: 896235

DATA PACKAGE BEAN SHEET

Date: 15-Jun-2011

* * * Registration Information * * *

Registration: 2382-RIT - EFFITIX TROPICAL SOLUTION FOR DOGS

Company: 2382 - VIRBAC AH, INC.

Risk Manager: RM 10 - Richard Gebken - (703) 305-6701 Room# PYt S-7237

Risk Manager Reviewer: Bonaventure Akinlosotu BAKINLOS

Sent Date: 19-May-2011 Calculated Due Date: 19-Nov-2011 Edited Due Date:

Type of Registration: Product Registration - Section 3

Action Desc: (R310) NEW PRODUCT;NON-FAST TRACK (INCLUDES REVIEWS OF PRODUCT CHEMIST

Ingredients: 109701, Permethrin(44.88%)

129121, Fipronil(6.01%)

R310 #29040

* * * Data Package Information * * *

Expedite: ○ Yes ● No Date Sent: 15-Jun-2011 Due Back:

DP Ingredient: 109701, Permethrin

129121, Fipronil

DP Title: prod chem

CSF Included: ● Yes ○ No Label Included: ● Yes ○ No Parent DP #:

Assigned To	Date In	Date Out	
Organization: RD / TRB			Last Possible Science Due Date: 20-Oct-2011
Team Name: CHEM			Science Due Date:
Reviewer Name:			Sub Data Package Due Date:
Contractor Name:			

* * * Studies Sent for Review * * *

Printed on Page 2

* * * Additional Data Package for this Decision * * *

No Additional Data Packages

* * * Data Package Instructions * * *

For your review:

MRID Nos. 484671- 01 to 08 & 10; and 48487301, for an R310, new fipronil/permethrin containing spot-on for dogs.

Thnx, B.A

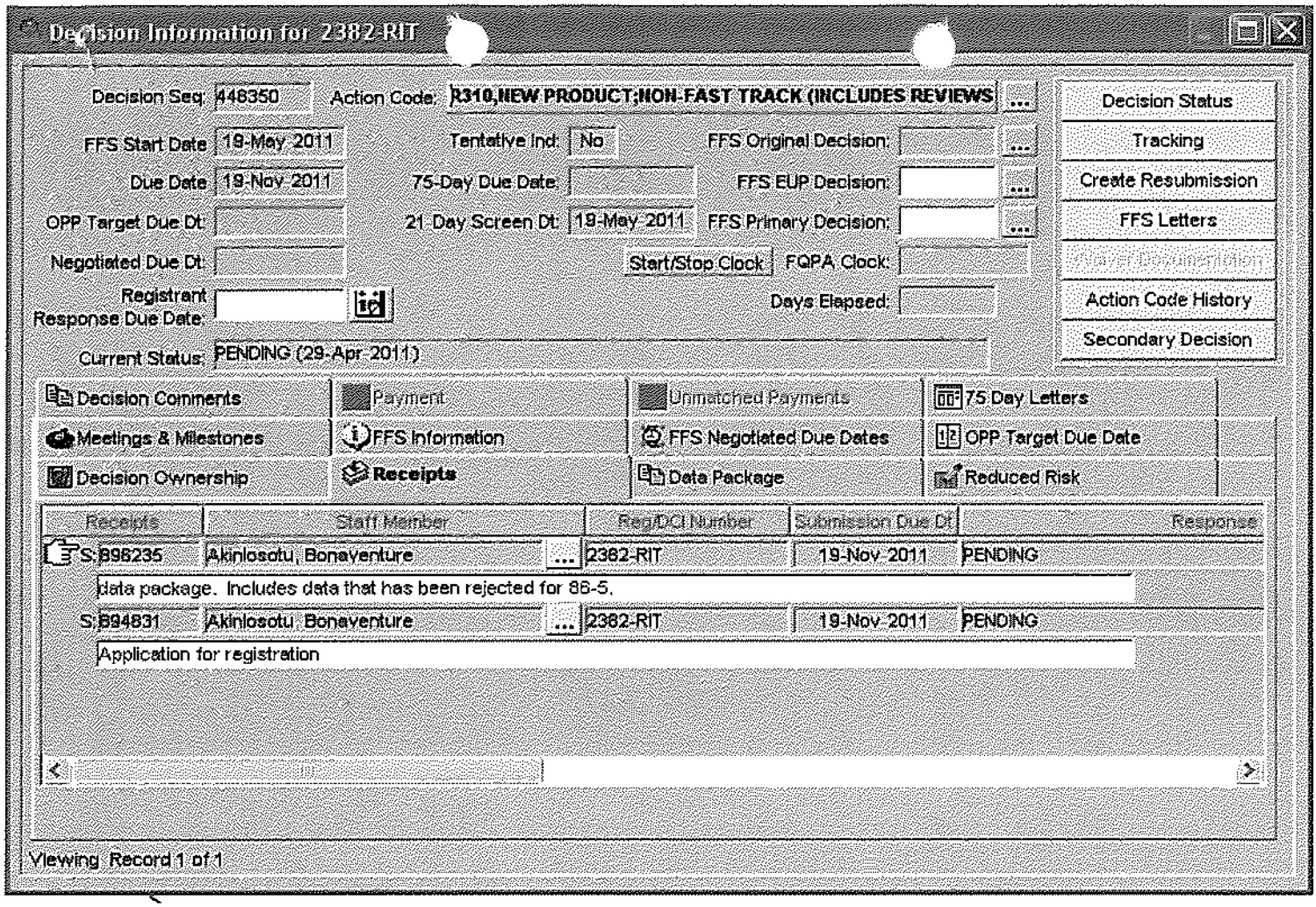
N/B:- Unreg tech source previously approved for use to register 2382-185 -186 / See enclosed data matrix.

Per Shyam, may need Corps A & B, and 5 batch analysis?

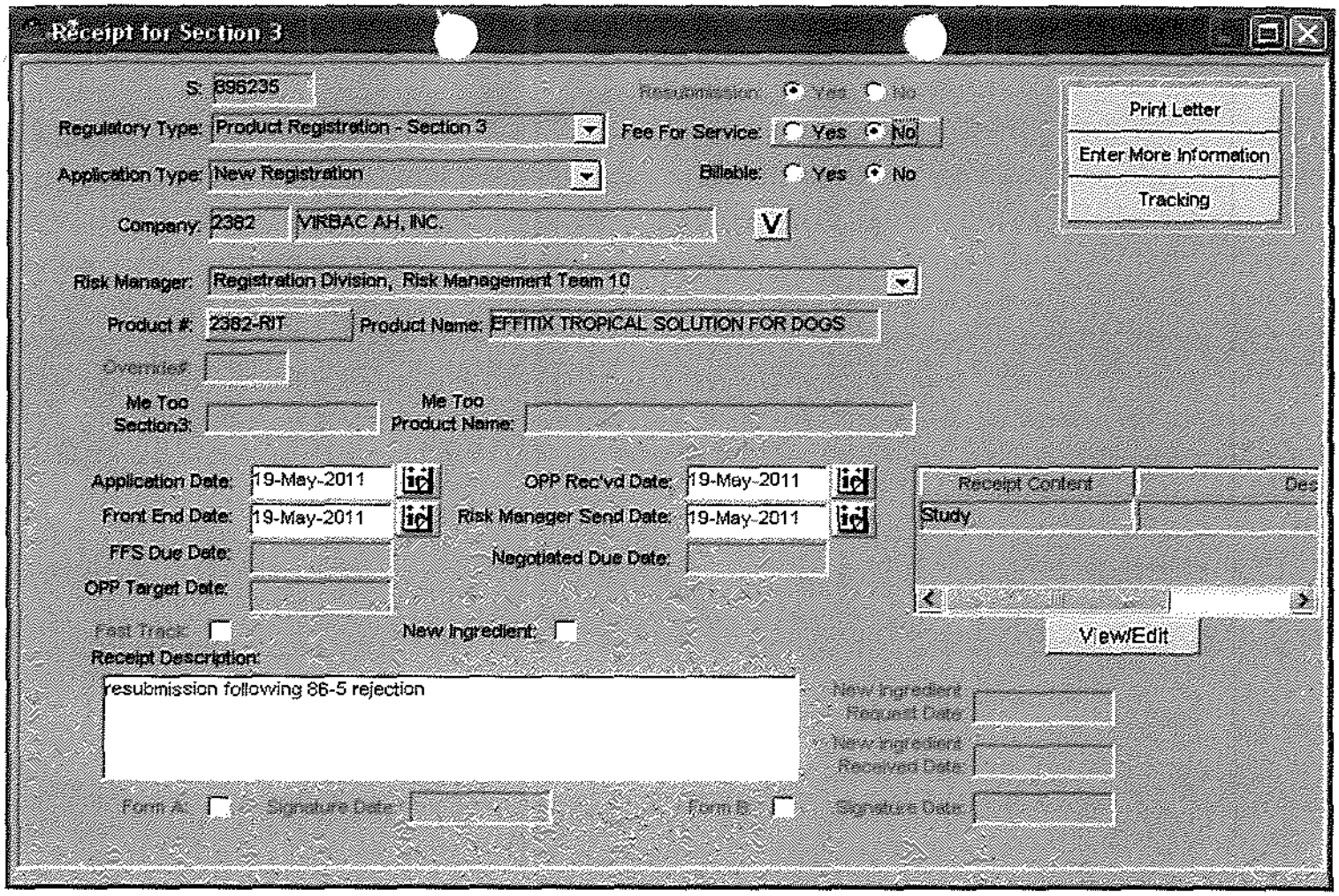
BA 605.0653 .8

DP#: (390814) *** Studies Sent for Review *** Decision#: (448350)

MRID	MRID Status	Citation Reference	Guideline
48467106		Habeck, C. (2009) Project 104.05: Determination of the Flash Point: Final Report. Project Number: C24732. Unpublished study prepared by Harlan Laboratories, Ltd. 29 p.	830.6315/Flammability
48467102		Zepperitz, Ch. (2010) Project 104.05: Quantification of the Active Ingredients Fipronil and Permethrin in Five Batches by a Validated Method: Final Report. Project Number: C96541. Unpublished study prepared by Harlan Laboratories, Ltd. 44 p.	830.1800/Enforcement analytical method
48467103		Zepperitz, Ch. (2010) Project 104.05: Enforcement Analytical Method: Final Report. Project Number: C96552. Unpublished study prepared by Harlan Laboratories, Ltd. 34 p.	830.1800/Enforcement analytical method
48467104		Habeck, C. (2009) Project 104.05: Determination of Color, Physical State and Odor: Final Report. Project Number: C32753. Unpublished study prepared by Harlan Laboratories, Ltd. 26 p.	830.6304/Odor
48467101		Villard, I. (2011) Product Specific Chemistry for Efftix Topical Solution for Dogs. Project Number: VIRBAC/104/05/1. Unpublished study prepared by Virbac. 36 p.	830.1550/Product identity and composition
48467101		Villard, I. (2011) Product Specific Chemistry for Efftix Topical Solution for Dogs. Project Number: VIRBAC/104/05/1. Unpublished study prepared by Virbac. 36 p.	830.1750/Certified limits
48467107		Habeck, C. (2010) Project 104.05: Determination of the Storage Stability (Shelf-Life): Final Report. Project Number: C24697. Unpublished study prepared by Harlan Laboratories, Ltd. 79 p.	830.6304/Odor
48467101		Villard, I. (2011) Product Specific Chemistry for Efftix Topical Solution for Dogs. Project Number: VIRBAC/104/05/1. Unpublished study prepared by Virbac. 36 p.	830.1620/Description of production process
48467101		Villard, I. (2011) Product Specific Chemistry for Efftix Topical Solution for Dogs. Project Number: VIRBAC/104/05/1. Unpublished study prepared by Virbac. 36 p.	830.1600/Description of materials used to produce the product
48467102		Zepperitz, Ch. (2010) Project 104.05: Quantification of the Active Ingredients Fipronil and Permethrin in Five Batches by a Validated Method: Final Report. Project Number: C96541. Unpublished study prepared by Harlan Laboratories, Ltd. 44 p.	830.1700/Preliminary analysis
48467104		Habeck, C. (2009) Project 104.05: Determination of Color, Physical State and Odor: Final Report. Project Number: C32753. Unpublished study prepared by Harlan Laboratories, Ltd. 26 p.	830.6303/Physical state
48467107		Habeck, C. (2010) Project 104.05: Determination of the Storage Stability (Shelf-Life): Final Report. Project Number: C24697. Unpublished study prepared by Harlan Laboratories, Ltd. 79 p.	830.6320/Corrosion characteristics
48467107		Habeck, C. (2010) Project 104.05: Determination of the Storage Stability (Shelf-Life): Final Report. Project Number: C24697. Unpublished study prepared by Harlan Laboratories, Ltd. 79 p.	830.6317/Storage stability
48467107		Habeck, C. (2010) Project 104.05: Determination of the Storage Stability (Shelf-Life): Final Report. Project Number: C24697. Unpublished study prepared by Harlan Laboratories, Ltd. 79 p.	830.6303/Physical state
48467104		Habeck, C. (2009) Project 104.05: Determination of Color, Physical State and Odor: Final Report. Project Number: C32753. Unpublished study prepared by Harlan Laboratories, Ltd. 26 p.	830.6302/Color
48467110		Habeck, C. (2009) Project 104.05: Determination of the Relative Density: Final Report. Project Number: C24710. Unpublished study prepared by Harlan Laboratories, Ltd. 36 p.	830.7300/Density/relative density
4846710t		Villard, I. (2011) Product Specific Chemistry for Efftix Topical Solution for Dogs. Project Number: VIRBAC/104/05/1. Unpublished study prepared by Virbac. 36 p.	830.1650/Description of formulation process
48467107		Habeck, C. (2010) Project 104.05: Determination of the Storage Stability (Shelf-Life): Final Report. Project Number: C24697. Unpublished study prepared by Harlan Laboratories, Ltd. 79 p.	830.6302/Color
48467105		Habeck, C. (2009) Project 104.05: Determination of Oxidation/Reduction and Chemical Incompatibility with Certain Agents: Final Report. Project Number: C2472t. Unpublished study prepared by Harlan Laboratories, Ltd. 28 p.	830.6314/Oxidizing or reducing action
4846710t		Villard, I. (2011) Product Specific Chemistry for Efftix Topical Solution for Dogs. Project Number: VIRBAC/104/05/1. Unpublished study prepared by Virbac. 36 p.	830.1670/Discussion of formation of impurities
4848730t		Habeck, C. (2009) Project 104.05: Determination of the Viscosity: Final Report. Project Number: C24708. Unpublished study prepared by Harlan Laboratories, Ltd. 37 p.	830.7100/Viscosity
48467108		Habeck, C. (2009) Project 104.05: pH-Determination: Final Report. Project Number: C24743. Unpublished study prepared by Harlan Laboratories, Ltd. 28 p.	830.7000/pH



Received 6/15/2011 BA.


Receipt for Section 3
S: 896235
Resubmission: Yes No
Print Letter
Enter More Information
Tracking
Regulatory Type: Product Registration - Section 3
Fee For Service: Yes No
Application Type: New Registration
Billable: Yes No
Company: 2382 VIRBAC AH, INC.
Risk Manager: Registration Division, Risk Management Team 10
Product #: 2382-RIT Product Name: EFFITIX TROPICAL SOLUTION FOR DOGS
Overrides:
Me Too Section3:
Me Too Product Name:
Application Date: 19-May-2011
OPP Rec'vd Date: 19-May-2011
Front End Date: 19-May-2011
Risk Manager Send Date: 19-May-2011
FFS Due Date:
Negotiated Due Date:
OPP Target Date:
Receipt Content
Des
Study
Fast Track:
New Ingredient:
View/Edit
Receipt Description:
resubmission following 86-5 rejection
New Ingredient Request Date:
New Ingredient Received Date:
Form A:
Signature Date:
Form B:
Signature Date:

Rejected

(03)

Studies

Memorandum

Date: 5 / 31 / 11

To: PM 10, Regulatory Manager

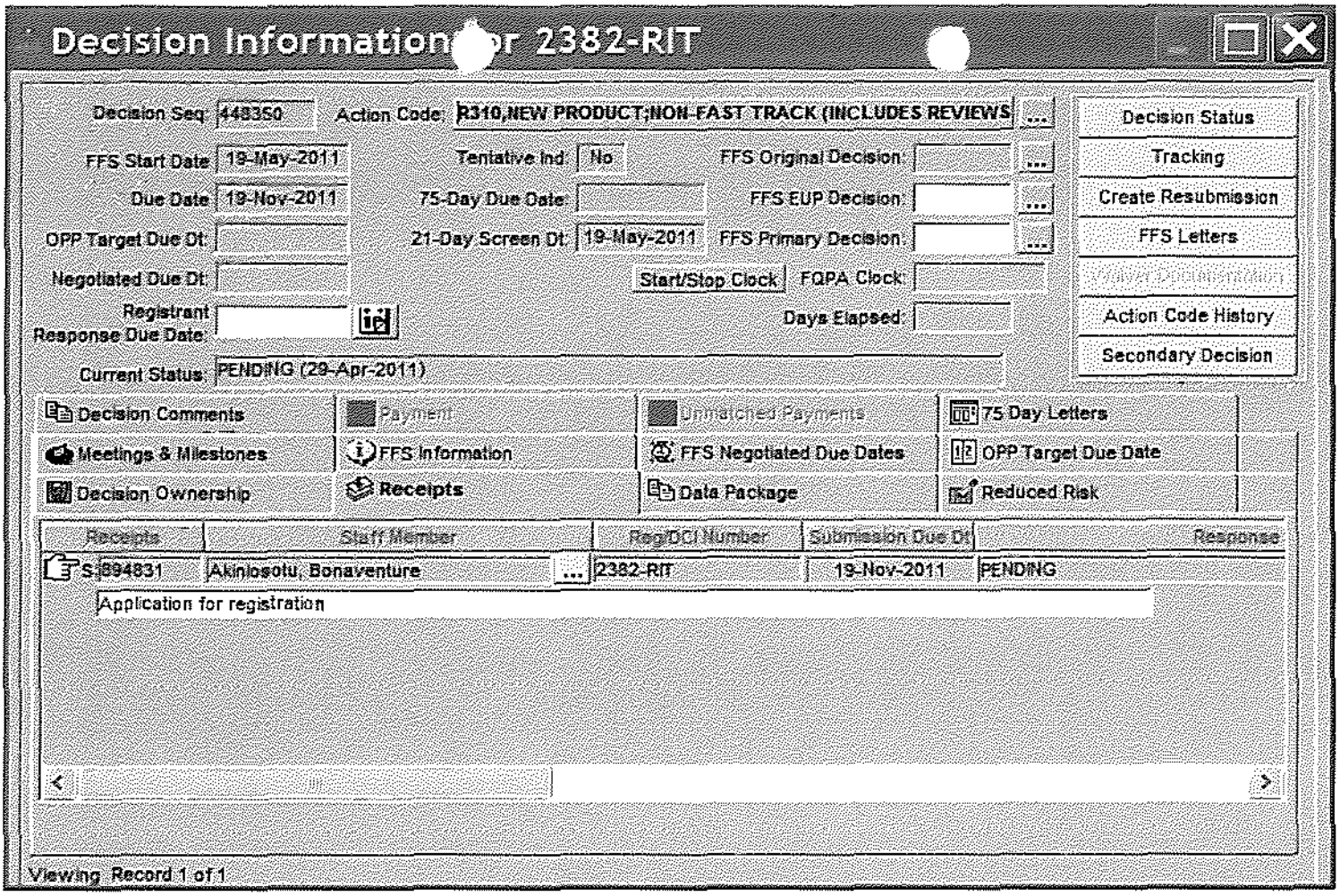
From: Information Services Branch, ITRMD

Your receipt of this data submission is not an indication that MRIDs for the enclosed studies have been posted to OPPIN.

We expect that it will be approximately 5 days from the above date before the study-level data is available in OPPIN.

If you have any questions about this process, please contact Teresa Downs (305-5363).

This is a:
- ☐ fully accepted submission
- ☒ partially accepted submission
- ☐ rejected submission



Received 5/17/2011

21-Day Screen Completed by Contractor

21-Day Expires on 5-19-11

Jacket # 2382-R1T
MRID# 484671

Content Screen: Recommend to Pass/Fail

86-5 Review: Pass/Fail/NA

Overall Status: Recommend to Pass/Fail

Transfer This Jacket to:

Stephen Schaible

PM 10 Y

16 May 2011 awat eom
2382-RIT

Memorandum

Date: 05 / 12 / 11

To: PM 10, Regulatory Manager

From: Information Services Branch, ITRMD

Your receipt of this data submission is not an indication that MRIDs for the enclosed studies have been posted to OPPIN.

We expect that it will be approximately 5 days from the above date before the study-level data is available in OPPIN.

If you have any questions about this process, please contact Teresa Downs (305-5363).

This is a:
- ☐ fully accepted submission
- ☒ partially accepted submission
- ☐ rejected submission

NEW APPLICATIONS

DATE: APR 28 2011

FILE NUMBER: 2382-RIT

FEP (OPPIN ENTRY) LV 4/29/2011
(Initial & date)

FILE ROOM: _____
(Initial & date)

SIG: _____
(Initial & date)

FILE ROOM: _____
(Initial & date)

✓ **ASSIGN TO PM** lo **(NO DATA)**

____ **JACKET TO SHELF (DATA)**

PRIA 2 – 21 Day Content Screen Review Worksheet

(EPA/OPP Use Only)

21 Day Screen Start Date: 4-28-11 3/23/09

Experts In-Processing Signature: B. R Date 5-2-11 Fee Paid: Yes ✓

Division management contacted on issues No_____Yes _____Date _____

EPA Reg. Number: 2382- RIT	EPA Receipt Date: 4-28-11

	Items for Review			Yes	No	N/A*
1	**Application Form** (EPA Form 8570-1)(link to form) signed & complete including package type			X		
2	**Confidential Statement of Formula** all boxes completed, form signed, and dated (EPA Form 8570-4) (Link to form)			X		
	a) All inerts (link to http://www.epa.gov/opprd001/inerts/), including fragrances, approved for the proposed uses (see Footnote A)	**yes**	**no**			
3	**Certification with Respect to Citation of Data** (EPA Form 8570-34) (Link to form) completed and signed (N/A if 100% repack)			X		
	Certificate and data matrix consistent			X		
	If applicant is relying on data that are compensable, is the offer to pay statement included. (see Footnote B)	**yes**	**no**			
	If applicable, is there a letter of Authorization for exclusive use only.					
4	**Formulator's Exemption Statement** (EPA Form 8570-27) (Link to form) completed and signed (N/A if source is unregistered or applicant owns the technical)			X		
5	**Data Matrix** (EPA Form 8570-35) (Link to form) both internal and external copies (PR 98-5) (Link to PR 98-5) completed and signed (N/A if 100% repack)			X		
		yes	**no**			
	a) Selective Method (Fee category experts use)	X				
	b) Cite-All (Fee category experts use)					
	c) Applicant owns all data (Fee category experts use)					
6	**5 Copies of Label** (link to **http://www.epa.gov/oppfead1/labeling/lrm/**) **(Electronic labels on CD are encouraged and guidance is available)**(link to http://www.epa.gov/pesticides/regulating/registering/submissions/index.htm#labels)			X		

7	**Is the data package consistent with PR Notice 86-5** (link to PRN 86-5)		X	
8	**Notice of Filing (link to http://www.epa.gov/pesticides/regulating/tolerance_petitions.htm) included with petitions (link to http://www.epa.gov/pesticides/regulating/tolerances.htm)**			X
9	**If applicable for conventional applications, reduced risk rationale (link to http://www.epa.gov/opprd001/workplan/reducedrisk.html)**			X
10	**Required Data (link to http://www.epa.gov/pesticides/regulating/data_requirements.htm) and/or data waivers. See Footnote C.**			
	a) List study (or studies) not included with application			

KC 5/12

Comments:

- Inerts approved for non-food use.
- Associated studies (MRID 481671) have not passed 86-5 review:
  - Vol 10: pgs 20, 21, 23 & 24 are illegible
  - Vol 17: pg 59 illegible
  - Vol 25: pg 25 is missing replace 5 Pages

Registrant was called on 5/3/11 and 5/4/11 and sent an email detailing the corrections that needed to be made but no response was received before the deadline. Additionally, after obtaining alternate contact information on 5/12/11 a third call was made but there was no response.

Jacket documentation: Pass
86-5: fail (rejection letter saved to H:// done)

* N/A – Not Applicable

Footnotes

A. During the 21 day initial content review, all CSFs will be reviewed to determine whether all inerts listed, including fragrances, are approved for the proposed uses. If an unapproved inert is identified, the applicant must either 1) resolve the inert issue by, for example, removing the inert, substituting it with an approved inert, submitting documentation that EPA approved the inert for the proposed pesticidal uses, correcting mistakes on the CSF, etc. or 2) provide the data to support OPP approval of the inert or 3) withdraw the application. Removing or substituting an inert ingredient will require a new CSF and may require submission of data. All information, forms, data and documentation resolving the inert issue must have been received by the Agency or the application withdrawn within the 21 day period, otherwise, the Agency will reject the application as described below.

To successfully complete this aspect of the 21 day initial content screen, applicants are **strongly encouraged** to verify that all inert ingredients have been approved for the application's uses **even if a product is currently registered** by consulting the inert Web

site [link to http://www.epa.gov/opprd001/inerts/lists.html] and if the inert is not approved, to **obtain the necessary inert approval prior to submitting an application to register a pesticide product containing that inert ingredient.** Some inert ingredients are no longer approved for food uses or certain types of uses. The name and/or CAS number on a CSF must match the name and CAS number on this web site. Simple typographical errors in the name or CAS number have resulted in processing delays.

If an inert is not listed on the inert ingredient web site and the applicant believes that the inert has been approved, the applicant should contact the Inert Ingredient Assessment Branch (IIAB) at inertsbranch@epa.gov and resolve the issue. Copies of the correspondence with IIAB resolving the issue should accompany the application. All new inerts except PIP inerts are reviewed by IIAB. The IIAB should also be contacted for any questions on what supporting data needs to be submitted for and the Agency's inert review process. Questions on PIP inerts should be directed to the Chief of Microbial Pesticides Branch [Link to http://www.epa.gov/oppbppd1/biopesticides/contacts_bppd.htm].

When a brand, trade, or proprietary name of an inert ingredient is listed on a CSF, additional information such as an alternate name of the inert, CAS number or other information [link to http://www.epa.gov/opprd001/inerts/tips.pdf] must also be included to enable the Agency to determine if it has been approved. Each component of an inert mixture (including a fragrance) must be identified. In some cases, the supplier of the mixture or fragrance may need to provide this information to the Agency. Prior to the Agency's receipt of an application, applicants must arrange with a proprietary mixture or fragrance supplier to provide the component information to the Agency or promptly upon EPA's request. If the inert ingredients in a proprietary blend (including fragrances) cannot or are not identified or provided within the 21-day content review period, the Agency will reject the application.

During the 21 day content review, applicants should submit information to the individual identified by the Agency when the applicant is informed of an unapproved inert.

Unapproved Inerts Identified on CSFs

All applications except conventional new products and PIPs

Once an unapproved inert is identified on a CSF, the Agency will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or

2. Submit the information and data needed for the Agency to approve the unapproved inert. If this option is selected and implemented, the Agency may request an extension in the PRIA decision review timeframe to accommodate the inert review/approval process;

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of these options is selected and implemented by the applicant within the 21 day content review period, the Agency will reject the application and retain 25% of the full fee of the category identified.

Conventional New Product Applications

When the Registration Division identifies an unapproved inert on a CSF with an application for a new product that the applicant has not identified as requiring an inert approval (R311, R312 or R313), it will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or

2. Submit the information and data needed for the Agency to approve the unapproved inert, including any required petition to establish or amend a tolerance or exemption from a tolerance. (This option may change the PRIA category for the application, which could require a longer decision review time and a larger fee. If additional fees are due, they must be received by the Agency within the 21 day content review period.)

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21-day content-review period, the Agency will reject the application and retain 25% of the appropriate fee for the new product-inert approval category.

PIP Applications

When the Biopesticide and Pollution Prevention Division identifies an unapproved inert on a PIP CSF and a request to approve the inert does not accompany the application, it will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the spelling or name of the inert to that in 40 CFR 174, or providing documentation that the inert has been approved; or

2. Submit the information and data needed for the Agency to approve the unapproved inert. If an inert ingredient tolerance exemption petition is required, the petition must be received by the Agency and the B903 fee paid within the 21 day period. If this option is selected and implemented, the Agency will discuss harmonizing the timeframe for both actions.

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21 day content review period, the Agency will reject the application and retain 25% of the fee.

B. A policy on documentation of offers to pay is still being developed, however, for a me-too or fast track (similar/identical) new product, R300 or A530, an application without the necessary authorizations of offers to pay will be placed into either R301 or A531. The Agency recommends that authorizations of offers to pay be submitted with other PRIA applications to avoid delays in the Agency's decision.

C. Biopesticide applicants are advised to contact the Agency and discuss study waivers prior to submitting their application to the Agency. Documentation of such discussions should be submitted with the study waiver.

Fee for Service

{894831/~

This package includes the following

- ◉ New Registration
- ○ Amendment

☑ Studies? ☐ Fee Waiver?

☐ volpay % Reduction: ___

for Division

- ○ AD
- ○ BPPD
- ◉ RD

Risk Mgr. 10

Receipt No. S-	894831
EPA File Symbol/Reg. No.	2382-RIT
Pin-Punch Date:	4/28/2011

☐ This item is NOT subject to FFS action.

Action Code:

Requested: R310

Granted: R310

Amount Due: $ 4,807. ea

Parent/Child Decisions:

☒ Inert Cleared for Intended Use ☒ Uncleared Inert in Product

Reviewer: [signature] Date: 4-25-11

Remarks:

ISB'S Front-end PRIA Completeness Screen

Draft 3; 10/25/07

EPA Receipt Date: APR 28 2011	EPA Reg. Number: 2382 - RIT

	Check List Item	Yes	No	N/A
1	Has the **PRIA Fee been Paid**; is a copy of the check or Pay.gov receipt included in the Submission Package?	X		
2	Is an **Application Form** (EPA Form 8570-1) Included in the Submission Package, is it completely filled out and signed including package type?	X		
3	Is a **Confidential Statement of Formula** (EPA Form 8570-29) Included in the Submission Package, is it completely filled out and signed (boxes 1-21)?	X		
4	Is a **Formulator's Exemption Statement** (EPA Form 8570-27) Included in the Submission Package?	X		
5	Is a **Certification with Respect to Citation of Data** (EPA Form 8570-34) Included in the Submission Package?	X		
6	Is a **Data Matrix** (EPA Form 8570-35) Included in the Submission Package?	X		
7	Is a **Label** Included in the Submission Package?	X		
8	Are **Data** Included in the Submission Package?	X		
9	**Is the Submission an Amendment?**			

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Avenue NW
Washington, D.C. 20460

EPA Reg. Number:	Date of Issuance:
2382-187	11/18/2011

Term of Issuance: Conditional

Name of Pesticide Product: Effitix™ Tropical Solution for Dogs

NOTICE OF PESTICIDE:
X Registration
Reregistration
(under FIFRA, as amended)

Name and Address of Registrant (include ZIP Code):

Virbac Animal Health, Inc.
P.O. Box 162059
Fort Worth, TX 76161

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is registered in accordance with FIFRA sec 3(c)(7)(A), contingent on the following:

1. Make the following labeling changes before releasing the product for shipment:
   a. Revise the EPA Registration Number to read: "EPA Registration No. 2382-187".

Signature of Approving Official:	Date:
See page 4 Richard Gebken, Product Manager (RM 10) Insecticide Branch Registration Division (MC 7505P)	November 18, 2011

EPA Form 8570-6

2. This registration is time-limited and expires two years from the date this product is first released for shipment.

   You must provide the Agency with a projected "release for shipment date", in writing within 30 days of the date of this Notice of Registration. The Agency will calculate the expiration date based on the projected "release for shipment date" until an actual release for shipment date is provided in writing.

3. Only one basic confidential statement of formula (CSF) will be on file for this product at any time (i.e., no alternate formulations or minor formulation amendments will be submitted and/or approved for this product, except to allow for alternate sources of any individual inert ingredient).

4. If applicable, you must submit the following data within the timeframe described below:
   Within sixteen (16) months of the date on this Notice of Registration, provide to the Agency acceptable data packages for Guideline Studies: OPPTS 830.6320 (Corrosion Characteristics) and OPPTS 830.6317 (Storage Stability).

   <u>Acute Dermal Sensitization Study:</u> Within 60 days of this NOR, acceptable positive control data (See copy of DER).

5. You must submit quarterly enhanced incident reports and quarterly sales information in doses sold for this product for the quarter that begins on April 1, 2012.

   The quarterly reports are due two months after the end of each quarter. Please flag any Confidential Business Information CBI) as such. Enhanced incident reporting should be submitted to the Product Manager. Quarterly sales information should be submitted to the Registration Division, Immediate Office (attn: Kimberly Nesci).

   The following is a list of information that must be included in the quarterly reports for each incident:

   EPA Registration Number
   Product name (brand name)
   Lot #
   Where purchased: internet, store, Veterinarian
   Active Ingredient(s)
   Weight range for product

   Date on which incident occurred. (mm/dd/yyyy)
   State in which the incident occurred. (standard 2 letter abbreviation)
   Registrant case #

   Species: dog, cat, other (specify)
   Breed: (as reported by pet owner)
   Age: months or years
   Sex: M, F, or neutered
   Weight: pounds

Primary Route of Exposure: dermal, oral, other animal, inhalation, other
Body System: neurological, dermatological, GI, respiratory, ocular, other Major signs noted with separate column for each sign, using standard terminology
Time to Onset: (hours, days)
Treated by veterinarian: yes or no
First time product used: yes or no
Misuse: use on incorrect species, overdose, too frequent dosing, other (describe)
Any known precondition
EPA Severity Code: death, major, moderate, minor
Outcome: died, recovered, still treated, unknown

6. Along with the enhanced incident reporting, you must submit an analysis of all incidents seen, to include the following details:

   a. All minor dermal and ocular irritation reports.
   b. Summary table for dogs showing number of incidents of each severity code for each route of exposure. Each incident should only be reported once. If one incident has several routes of exposure, the order should be ocular > oral > dermal. In other words, an incident with both oral and dermal exposure would be reported as oral exposure, and an incident with both ocular and oral exposure would be reported as ocular exposure.
   c. A similar summary table for cats (misuse or secondary exposure) showing number of incidents of each severity code for each route of exposure.
   d. Summary table for dogs and table for cats showing number of incidents that are believed due to secondary exposure (e.g., multi-pet households).
   e. A summary table for dogs showing number of incidents for each severity code for these age ranges: <3 months, 3-6 months, 6-9 months, 9-12 months, 1 yr, 2 yr, 3 yr, 4 yr, 5 yr, 6 yr, 7 yr, 8 yr, 9 yr, 10 yr, 11 yr, 12 yr, 13 yr, 14 yr, 15 yr, >15 yr.
   f. A summary table showing the number of dog incidents for each severity code for each pet weight range on the product label.
   g. A summary table for dog weight showing number of incidents for each product weight range. This table should show number of incidents in dogs weighing less than that product weight range, number of incidents in dogs in lower half of weight range, number of incidents in dogs in upper half of weight range, and dogs weighing more than the product weight range.
   h. Table showing number of incidents for each dog breed.
   i. Table showing number of incidents in dogs for each clinical sign.
   j. Table showing number of incidents in dogs for each organ system.
   k. Report aggregate incidents, but do not combine moderate and minor incidents.

7. You must submit and/or cite all data required for registration of your product under FIFRA Section 3(c)(5) when the Agency requires all registrants of similar products to submit such data, and submit acceptable responses required for re-registration (registration review) of your product under FIFRA section 4.

If EPA determines that future mitigation measures are necessary for all pet spot-on products, the Agency will inform all registrants concerned. If mitigation measures are necessary, EPA may take regulatory action.

Two copies of the finished labeling must be submitted prior to releasing the product for shipment. If you fail to comply with the above stated conditions, the registration will be subject to cancellation in accordance with FIFRA sec. 6(e) and/or automatically expire. Your release for shipment of the product constitutes your acceptance of these conditions.

A copy of your label stamped "Accepted with Comments" is enclosed for your records. If you have any questions concerning this action, please contact me or Dr. B. A. Akinlosotu via (703) 605-0653 or akinlosotu.bonaventure@epa.gov.

Sincerely,

Richard Gebken,
Product Manager (RM 10)
Insecticide Branch
Registration Division (MC 7505P)

Enclosures
Stamped Label

Virbac's Master Label

Date 16NOV11 Version US-9 EPA Reg. No. 2382-RIT
Fipronil+Permethrin Topical Solution for Dogs

Optional text appears in brackets.

EFFITIX™ TOPICAL SOLUTION FOR DOGS

Alternate brand names:

(EFFIX™ TOPICAL SOLUTION FOR DOGS)

(EFFICANIX™ TOPICAL SOLUTION FOR DOGS)

(EFFIPROTIX™ TOPICAL SOLUTION FOR DOGS)

FOR USE ONLY ON DOGS 12 WEEKS OLD OR OLDER (WEIGHING UP TO 22.9 LBS, WEIGHING 23 TO 44.9 LBS, WEIGHING 45 TO 88.9 LBS, WEIGHING 89 TO 132 LBS)

ACTIVE INGREDIENTS:

Fipronil	6.01%
Permethrin*	44.88%
OTHER INGREDIENTS:	49.11%
TOTAL:	100.00%

* cis/trans ratio: maximum 55% (±) cis and minimum 45% (±) trans

ACCEPTED
With COMMENTS
In EPA Letter Dated:
NOV 18 2011
Under the Federal Insecticide, Fungicide and Rodenticide Act, As amended, for the pesticide Registered under EPA Reg. No:
2382-187

KEEP OUT OF REACH OF CHILDREN

CAUTION

READ ENTIRE LABEL BEFORE EACH USE

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

HAZARDS TO HUMANS

Harmful if swallowed. Causes eye irritation. Avoid contact with skin, eyes, or clothing. Wash hands thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco, or using the toilet.

HAZAROS TO DOMESTIC ANIMALS

For external use on dogs ONLY.

DO NOT USE ON CATS – IF INGESTED BY CAT THAT ACTIVELY GROOMS A RECENTLY TREATED DOG, THIS PRODUCT MAY HAVE SERIOUS HARMFUL EFFECTS. IF THIS OCCURS, CONTACT YOUR VETERINARIAN IMMEDIATELY.

Do not use on dogs under 12 weeks of age. Individual sensitivities, while rare, may occur after using ANY pesticide product. Dogs may experience some temporary irritation at the site of product application. If signs of sensitivity occur, bathe your pet with mild soap or shampoo and rinse with large amounts of water. If signs of sensitivity occur and persist, contact a veterinarian immediately. If your dog has an unusual reaction to the initial application, consult a veterinarian before repeating application. Certain medications can interact with pesticides. Consult a veterinarian before using on medicated, debilitated, aged, pregnant or nursing dogs, or animals known to be sensitive to pesticide products.

FIRST AID	
IF SWALLOWED:	• Call a poison control center or doctor immediately for treatment advice. • Have person sip a glass of water if able to swallow. • Do not induce vomiting unless told to do so by a poison control center or doctor. • Do not give anything to an unconscious person.
IF IN EYES:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
IF ON SKIN OR CLOTHING :	• Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes. • Call a poison control center or doctor for treatment advice.
Have product container or label with you when calling a poison control center or doctor, or going for treatmenL You may also contact the Hotline number 1-800-338-3659 for human or veterinary health concerns, emergency medical treatment information or pesticide incidents.	

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in any manner inconsistent with its labelling. Do not allow children to apply product. TO PREVENT HARM TO YOU AND YOUR DOG, READ ENTIRE LABEL AND DIRECTIONS BEFORE EACH USE. FOLLOW ALL DIRECTIONS AND PRECAUTIONARY STATEMENTS CAREFULLY. FOR EXTERNAL USE ON DOGS ONLY. DO NOT USE ON CATS OR RABBITS. DO NOT USE ON OTHER ANIMALS.
DO NDT USE ON CATS.
FOR EXTERNAL USE DN DOGS ONLY. Do not use on dogs under 12 weeks of age. Do not split tubes between dogs. Do not use multiple tubes on one dog. Weigh your dog to be sure you are applying the right dose formulated for the weight of your dog. Overdosing your dog can result in serious illness. Do not bathe your dog within the first 24 hours after the product has been applied. If your dog is exhibiting signs of and/or is being treated for skin problems, talk to your veterinarian before applying any topical flea and tick control product.

Do not apply more often than once a (per) month (every 30 days).

For use in DOGS (12 weeks old or older). To repel and kill fleas, ticks, and mosquitoes; to kill lice and to aid in control of mites; to repel and prevent blood feeding by biting flies. Apply monthly according to directions.

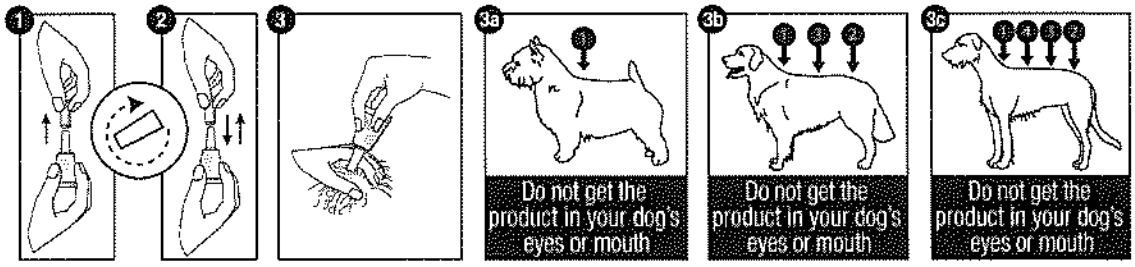
APPLICATION DIRECTIONS

1. Remove one applicator from packaging.
   Hold applicator upright and remove cap.
2. Invert cap and place other end back onto applicator tip.
   Push cap down to break seal.
   Remove cap prior to treatment application.
3. Part dog's hair until skin is visible.
   Place applicator tip directly against exposed skin.

3a. For small dogs (12 weeks old or older) and weighing up to 22.9 lbs- Deposit entire contents by squeezing the entire applicator contents onto dog's skin, at a single site, between the shoulder blades as shown in diagram 3a.

3b. For medium dogs 23-44.9 lbs or large dogs 45-88.9 lbs- Apply the product evenly to three spots on the dog's back, starting between the shoulder blades and continuing on to the second and third spots as shown in diagram 3b, squeezing the applicator until empty.

3c. For extra large dogs 89-132 lbs- Apply the product evenly to four spots on the dog's back, starting between the shoulder blades and continuing on to the second, third and fourth spots as shown in diagram 3c, squeezing the applicator until empty.
Ensure that EFFITIX™ Topical Solution for Dogs is not applied superficially on dog's hair.



FREQUENCY OF APPLICATION
Fleas, ticks, (biting and chewing) lice infestations can be controlled with monthly applications of EFFITIX™ Topical Solution for Dogs. Biting flies and mosquitoes are (also) repelled by EFFITIX™ Topical Solution for Dogs.

Fleas: EFFITIX™ Topical Solution for Dogs can start killing adult fleas within 6 hours and lasts for (up to) a month. Apply monthly if your dog has fleas that may cause flea allergy dermatitis (FAO), or if re-infestation is likely.
Ticks: EFFITIX™ Topical Solution for Dogs can kill ticks for (up to) a month. Apply monthly where tick control is consistently needed.
Lice: EFFITIX™ Topical Solution for Dogs can kill biting and chewing lice for (up to) a month. Apply monthly where lice control is consistently needed.
Mites: EFFITIX™ Topical Solution for Oogs aids in (the) control of (sarcoptic mange)/(mite infestations that may cause sarcoptic mange).
Biting flies and Mosquitoes: When applied monthly, EFFITIX™ Topical Solution for Dogs (prevents blood feeding by) (and) (repels) biting flies and mosquitoes for up to 4 weeks (a [one[month). Kills mosquitoes for up to four weeks (a [one) month).

Notes: Wait at least 30 days before re-application of EFFITIX™ Topical Solution for Dogs. Avoid contact with treated area until dry.

STORAGE ANO DISPOSAL

Do not contaminate water, food, or feed by storage and disposal.

STORAGE: Store unused product in original container only, out of reach of children and animals.

PESTICIOE fCONTAINER DISPOSAL: If empty: Nonrefillable. Oo not reuse or refill this container. Offer for recycling, if available. **If partially filled**: Call your local solid waste agency for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND DISCLAIMER

VIRBAC warrants this product only if it is used, stored and handled in accordance with the label instructions. The buyers and users are solely responsible for all risks of use and handling of this product when such use and handling are contrary to or differ from the label instructions. To the extent permitted by applicable law, any damages arising from a breach of this warranty shall be limited to direct damages only and shall not include any type of consequential damages.

How supplied: For easy and convenient application, EFFITIX™ Topical Solution for Dogs is available in sizes for small dogs 12 weeks old or older up to 22.9 lbs (0.034 fl oz)/(t.0 mL), medium dogs 23-44.9 lbs (0.068 fl oz)/(2.0 mL), large dogs 45-88.9 lbs (0. t35 fl oz)/(4.0 mL), and extra large dogs 89-132 lbs (0.203 fl oz)/(6.0 mL).

Net Contents: t (3, 6 or 36) single-dose applicator(s) per package containing tmL (2mL, 4mL or 6mL)/ 0.034 fl oz (0.068 fl oz, 0. f35 fl oz, 0.203 fl oz) (of solution).

(Detachable) calendar (monthly application) reminder stickers (with illustration of dog or puppy)

EPA Reg. No. 2382-RIT
EPA Est. No. 2382-FRA-1

VIRBAC AH, INC.
PO BOX 162059
FORT WORTH TX 76161
1-800-338-3659

Made in France
EFFITIX™ is a trademark of Virbac S.A.
Questions or comments?
Call: 1-800-338-3659

{Text for Front Panel, Back Panel, Inside Flap and Side Panel}

See package insert(s) for directions for use and frequency of application
See package insert for directions for use and storage and disposal
See package insert for frequency of application and storage and disposal
Open resealable label for directions for use
Open resealable label for directions for use and storage and disposal
See back panel for additional precautionary statements
See package insert(s) for frequency of application
See enclosed insert(s) for directions for use and storage and disposal
See enclosed insert(s) for directions for use
Lift here to open (LIFT HERE TO OPEN)
For Use on Dogs ONLY
Use ONLY on dogs
See inside flap for directions for use

{Text for Foil of Blister package}

Virbac
EFFITIX™ Topical Solution For Dogs
Only for use on dogs up to 22.9 lbs (23-44.9 lbs, 45-88.9 lbs, 89-132 lbs)/0.034 fl oz (0.068 fl oz, 0.135 fl oz, 0.203 fl oz) (1.0 mL, 2.0 mL, 4.0 mL, 6.0mL)
Contains fipronil (6.01%) and permethrin (44.88%)
KEEP OUT OF REACH OF CHILDREN
CAUTION
See full label for additional directions
EPA Reg. No. 2382-XXX
DO NOT USE ON CATS
CAT PROHIBITION ICON

{Text for Applicator Tube}

Virbac
EFFITIX™
Topical Solution For Dogs
Only for use on dogs
up to 22.9 lbs (23-44.9 lbs, 45-88.9 lbs, 89-132 lbs)
0.034 fl oz (0.068 fl oz, 0.135 fl oz, 0.203 fl oz) [/ 1.0 mL (2.0 mL, 4.0 mL, 6.0mL)]
Contains fipronil (6.01%)
and permethrin (44.88%)
KEEP OUT OF REACH OF CHILDREN
CAUTION
See full label for additional directions
DO NOT USE ON CATS
EPA Reg. No. 2382-XXX
CAT PROHIBITION ICON

MARKETING CLAIMS

[Multiple infestations]

- For convenient, quick-acting, long-lasting control of fleas, ticks, mosquitoes and lice.
- (When) Applied topically on a monthly basis, EFFITIX™ Topical Solution for Dogs repels and kills fleas, ticks and mosquitoes, kills (biting, chewing) lice, aids in control of mites and repels (and inhibits blood feeding) by biting flies and mosquitoes.
- For easy and convenient application, EFFITIX™ Topical Solution for Dogs is available in sizes for small dogs (12 weeks old or older) and up to 22.9 lbs (0.034 fl oz)(1.0 mL), medium dogs 23-44.9 lbs (0.068 fl oz) (2.0mL), large dogs 45-88.9 lbs (0.135 fl oz) (4.0 mL), and extra large dogs 89-132 lbs (0.2031 oz) (6.0 mL).
- EFFITIX™ Topical Solution for Dogs contains the active ingredients fipronil and permethrin, which control infestations caused by fleas, ticks and lice; repel (against) biting flies, and repel and kill mosquitoes.
- Kills fleas, ticks, lice, and mosquitoes, repels biting flies and mosquitoes
- Repels and kills fleas and ticks
- Repels fleas, ticks, biting flies and mosquitoes
- Kills, repels and detaches ticks
- For the control and prevention of flea [and lice] infestations
- Flea, tick, (biting and chewing) lice infestations can be controlled with monthly applications of EFFITIX™ Topical Solution for Dogs. Biting flies and mosquitoes are (also) repelled by EFFITIX™ Topical Solution for Dogs.
- Monthly application against fleas, ticks and mosquitoes
- Kills fleas, ticks and mosquitoes for (up to) one month
- Monthly application is recommended for control and prevention of fleas, ticks and mosquitoes
- Long lasting flea, tick and mosquito control for your pet
- EFFITIX™ Topical Solution for Dogs is indicated for the prevention and control of fleas, ticks, mosquitoes, and lice on dogs 12 weeks of age and older
- Helps to relieve your dog's pain (discomfort) by controlling flea, tick and lice infestations
- Kills the vectors that may transmit Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, hepatozoonosis and heartworm disease.
- Kills fleas, ticks, mosquitoes, lice, and aids in control of mites
- Kills and repels fleas, ticks, and mosquitoes.

[Fleas]

- Fleas: EFFITIX™ Topical Solution for Dogs can kill adult fleas in 6 hours (and lasts) for (up to) one [a] month. Apply monthly if your dog has fleas that may cause flea allergy dermatitis (FAD), or if reinfestation is likely.
- Kills newly emerged adult fleas prior to egg laying
- Kills fleas (within 6 hours) that may transmit bartonellosis, (tularemia) (and tapeworm)
- Kills fleas (within 6 hours) that may transmit diseases, including bartonellosis, (tularemia) (and tapeworm infestations)
- Kills fleas (within 6 hours) that may transmit diseases, including bartonellosis and tularemia
- Rapid kill of fleas is important in the prevention of disease transmission by (these) parasites
- Acts to kill fleas that may transmit disease, such as bartonellosis and tularemia

- Kills fleas that may serve as an intermediate host for tapeworms (*Dipylidium caninum*)
- Kills fleas that may serve as an intermediate host for cysticercoids of tapeworms
- Kills fleas that may serve as hosts for life cycle intermediates of tapeworms
- Kills (adult) fleas (within 6 hours) that may cause Flea Allergy Dermatitis (FAD) (or) (flea-bite anemia)
- Fleas do not have to bite to die
- Controls highly [irritating] [annoying] [flea] bites
- EFFITIX™ Topical Solution for Dogs rapidly kills fleas that may cause FAD (Flea Allergy Dermatitis)
- The successive feeding activity of fleas on dogs may elicit a hypersensitivity skin disorder known as Flea Allergy Dermatitis (FAD)
- EFFITIX™ Topical Solution for Dogs kills fleas and may reduce the incidence of Flea Allergy Dermatitis (FAD)
- Kills adult fleas for up to one month (4 weeks)
- Kills fleas
- Easy to apply, control of (for) fleas that lasts up to 1 month (4 weeks)
- EFFITIX™ Topical Solution for Dogs kills fleas on your dog
- Once a month topical flea control for dogs 12 weeks of age or older
- EFFITIX™ Topical Solution for Dogs is indicated for the prevention and control of fleas on dogs 12 weeks of age and older
- One application prevents further flea infestations for up to (4 weeks) (a (one) month)
- Monthly treatment (all year] is recommended for control and prevention of fleas
- Provides ongoing protection against fleas and the diseases they may transmit for one month
- Stops existing flea infestations by rapidly killing adult fleas
- Kills fleas before they lay eggs
- Stops existing flea infestations by killing adult fleas
- Prevents (Stops] re-infestations by killing adult fleas (before they lay eggs)
- Treatment with EFFITIX™ rapidly kills fleas which may cause flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Controls flea problems
- Provides flea protection
- Use flea [prevention] [protection) year-round
- EFFITIX™ Topical Solution for Dogs controls flea infestation that may lead to painful skin irritation and bacterial infection

[Ticks]
- Ticks: EFFITIX™ Topical Solution for Dogs can kill ticks for (up to) a (one] month. Apply monthly where tick control is consistently needed.
- Kills and repels all stages of Brown dog ticks, American dog ticks, Lone Star ticks, and Deer ticks (that may transmit Lyme disease, Rocky Mountain Spotted Fever, babesiosis, ehrlichiosis and anaplasmosis)
- Kills ticks including Deer ticks (that may transmit Lyme disease), American dog ticks (that may transmit Rocky Mountain Spotted Fever), Brown dog ticks (that may transmit ehrlichiosis), and Lone Star ticks (that may transmit hepatozoonosis) for up to one month (4 weeks]
- Kills ticks including Deer ticks (that may transmit Lyme disease], American dog ticks (that may transmit Rocky Mountain Spotted Fever), and Brown dog ticks (that may transmit ehrlichiosis) for up to one month (4 weeks).
- Kills Brown dog ticks (*Rhipicephalus* spp), American dog ticks (*Dermacentor variabilis*), Deer ticks (*Ixodes* spp) and Lone Star ticks (*Amblyomma americanum*) for up to one month (4 weeks).
- Kills *Amblyomma americanum* (Lone Star ticks) for 4 weeks (for up to one month).
- Monthly application against ticks

[Mosquitoes and biting flies)
- Kills mosquitoes
- Kills mosquitoes for up to 28 days (four weeks) (a [one] month)
- Repels and inhibits blood feeding by biting flies and mosquitoes
- Biting flies and mosquitoes: When applied monthly, EFFITIX™ Topical Solution for Dogs (prevents blood feeding by) (and) (repels) biting flies and mosquitoes for (up to) 4 weeks (a (one] month)
- Repels and kills mosquitoes for up to four (4) weeks
- Prevents blood feeding by mosquitoes
- Repels and prevents (inhibits) blood-feeding by biting flies
- Repels and kills mosquitoes often before they have a chance to take a blood meal
- [(Prevents blood-feeding by) (Kills and repels)] mosquitoes
- Repels biting flies
- Repels [(annoying)(bothersome)(nuisance)] biting flies
- Inhibits [(annoying)(bothersome)(nuisance)) biting flies
- ((Prevents)(inhibits)[blood-feeding by biting flies
- Kills mosquitoes that may carry heartworm disease
- Repels and kills mosquitos (*Culex spp, Ochlerotatus spp, Aedes spp*) which may vector heartworm (*Dirofilaria immitis*] for one month

[Lice and Mites]
- Lice: EFFITIX™ Topical Solution for Dogs can kill biting and chewing lice for (up to) a [one] month. Apply monthly where lice control is consistently needed.
- Mites: (EFFITIX™ Topical Solution for Dogs) aids in (the) control of mites (that may cause sarcoptic mange)
- EFFITIX™ Topical Solution for Dogs aids in (the) control of mite infestations (that may cause sarcoptic mange).
- (When applied monthly,) EFFITIX™ Topical Solution for Dogs aids in (the) control of sarcoptic mange.
- Aids in (the) control of sarcoptic mange mite infestation
- Kills chewing and biting lice
- (Also) Kills lice and aids in control of mites

- Controls existing chewing/biting lice infestations
- Kills [(biting) (chewing)] lice
- For control and prevention of [(biting) (chewing)| lice (infestations)
- Stops existing [(biting) (chewing)[lice infestations
- Prevents and controls [(biting) (chewing)| lice (infestations)
- Provides control of |(biting) (chewing)] lice (infestations)
- Kills [(biting) (chewing)] lice and prevents further infestations
- For control and prevention of (infestations with) [(biting) (chewing)[lice

[Others]

- t (3, 6, 36) applicator(s) (tube[s]) 1.0 mL (2.0 mL, 4.0 mL, 6.0 mL)
- f (3, 6, 36) applicator(s) (tube|s]) 0.034 fl oz (0.068 fl oz, 0. t35 fl oz, 0.203 fl oz)
- t (3, 6, 36) applicator(s) (tube[s]) 0.034 fl oz [1.0 mL) (0.068 fl oz |2.0 mL), 0. f35 fl oz [4.0 mL], 0.203 fl oz |6.0 mL])
- t (3, 6, 36) applicator(s) (tube|s]) (each) containing 0.034 fl oz [t.0 mL] (0.068 fl oz [2.0 mL), 0. t35 fl oz [4.0 mL[, 0.203 fl oz [6.0 mL|)
- t (3, 6, 36) applicator(s) (tube[s])
- t (3, 6, 36) monthly dose(s) (application[s[]
- t (3, 6, 36) applicator(s) (tube[s]) f (3, 6, 36) month(ly) dose(s) (application(s)
- DO NOT USE ON CATS
- This product is only for use on dogs 12 weeks of age or older up to 22.9 lbs (weighing 23 to 44.9 lbs, weighing 45 to 88.9 lbs, weighing 89 to 132 lbs)
- Up to 22.9 lbs (weighing 23 to 44.9 lbs, weighing 45 to 88.9 lbs, weighing 89 to 132 lbs)
- Easy and convenient application (applications)
- Remains effective for a (one) month (4 weeks]
- Stops existing infestations and prevents establishment of new infestations
- Reinfestation of fleas, ticks and mosquitoes, (biting, chewing] lice and biting flies is prevented for a (one) month or longer
- Convenient topical treatment for dogs
- Quick onset of activity
- Persistent efficacy through 30 days
- Prevents (re-)infestation for one month
- Once monthly application
- Quick drying, non-greasy
- (Convenient) (to use) Easy (to apply) spot-on (topical) application
- Fragrance (odor) free
- No noticeable odors
- Single application lasts 4 weeks (one month) (30 days)
- Easy to use applicator makes treatment simple (trouble free, smooth) and comfortable for your pet
- Convenient, easy to apply topical solution
- Convenient, easy to apply and fragrance free topical solution
- Starts working by (on) contact
- (In) child-resistant packaging
- Convenient (to use), easy to apply (topical solution)
- EFFITIX™ Topical Solution for Dogs remains effective after bathing, shampooing, water immersion, or sunlight exposure.
- Waterproof (remains effective after bathing and swimming) for up to four weeks (a month) (one month)
- Remains effective after exposure to sunlight
- Remains effective even after bathing, water immersion, or exposure to rain or sunlight
- Remains effective even after bathing (and swimming)
- Remains effective after exposure to rain and/or sunlight
- Still works after bathing, swimming or exposure to sunlight
- Maintains residual efficacy after bathing and swimming
- Remains effective after bathing (and swimming) [(for a month) (for one month) (for up to four weeks)]
- For dogs that enjoy the outdoors
- For indoor and outdoor dogs
- Convenient topical treatment for dogs who enjoy the outdoors
- Formulated for dogs that love the outdoors
- For dogs that enjoy the outdoors
- Available from licensed veterinarians
- Illustration of flea life cycle
- Illustration of tick life cycle
- Illustration of mosquito life cycle
- Illustration of mite life cycle
- Illustration of louse life cycle
- Illustration of flea
- Illustration of tick
- Illustration of mosquito
- Illustration of mite
- Illustration of louse
- Picture or illustration of a dog (or puppy)
- Picture or illustration of the Virbac logo
- Picture or illustration of the primary package (applicator tubes)

Effitix PDF with no strikeouts
Jim Barron
to:
Bonaventure Akinlosotu
11/17/2011 01:11 PM
Hide Details
From: "Jim Barron" <jbarron@exponent.com>

To: Bonaventure Akinlosotu/DC/USEPA/US@EPA

2 Attachments

image003.jpg Effitix Master label resubmitted to EPA Nov 16 2011 ver 2.pdf

Bonaventure,

Per our telephone conversation, attached is a copy of the pdf version of the Effitix label with no strikeouts. It is derived from the same exact pdf file that you received from me yesterday.

Let me know if you need anything else or have any questions.

Thank you,

Jim Barron, Ph. D.
Managing Regulatory Consultant
Exponent®, Inc.
1000 Centre Green Way Suite 200
Cary, NC 27513

Office Telephone (919) 228-6479
Mobile Telephone (919) 534-6018

Facsimile (919) 228-6501
Email Address jbarron@exponent.com

Corrected Effitix Label-2382-RIT
Jim Barron
to:
Richard Gebken
11/16/2011 11:48 AM
Cc:
Bonaventure Akinlosotu, "Brenton Smith"
Hide Details
From: "Jim Barron" <jbarron@exponent.com>

To: Richard Gebken/DC/USEPA/US@EPA

Cc: Bonaventure Akinlosotu/DC/USEPA/US@EPA, "Brenton Smith" <brenton.smith@virbacus.com>

2 Attachments

image003.jpg Effitix Master label resubmitted to EPA Nov 16 2011.pdf

Richard and Bonaventure,

Please find attached the Effitix label with the following changes:

1. **All corrections and deletions requested in the efficacy review of Clayton Myers dated November 8, 2011.**
2. **According to PR 96-6, and confirmation from Richard, we have deleted the puppy claim and proposed a minimum age of 12 weeks for treatment with this product.**
3. **Bullets describing illustrations have been moved from page 4 to the end of MARKETING CLAIMS at request of R. Gross.**

Thank you for your help in registering this product.

Please let me know immediately if there are any other questions.

Jim Barron 919-462-9860 (

Jim Barron, Ph. D.

Virbac's Master Label

Date 16NOV11 Version US-9 EPA Reg. No. 2382-RIT
Fipronil+Permethrin Topical Solution for Dogs

Optional text appears in brackets.

EFFITIX™ TOPICAL SOLUTION FOR DOGS

Alternate brand names:

(EFFIX™ TOPICAL SOLUTION FOR DOGS)
(EFFICANIX™ TOPICAL SOLUTION FOR DOGS)
(EFFIPROTIX™ TOPICAL SOLUTION FOR DOGS)

FOR USE ONLY ON DOGS 12 WEEKS OLD OR OLDER (WEIGHING UP TO 22.9 LBS, WEIGHING 23 TO 44.9 LBS, WEIGHING 45 TO 88.9 LBS, WEIGHING 89 TO 132 LBS)

ACTIVE INGREDIENTS:	
Fipronil	6.01%
Permethrin*	44.88%
OTHER INGREDIENTS:	49.1 t%
TOTAL:	100.00%

* cis/trans ratio: maximum 55% (±) cis and minimum 45% (±) trans

KEEP OUT OF REACH OF CHILDREN

CAUTION

READ ENTIRE LABEL BEFORE EACH USE

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

HAZARDS TO HUMANS

Harmful if swallowed. Causes eye irritation. Avoid contact with skin, eyes, or clothing. Wash hands thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco, or using the toilet.

HAZARDS TO DOMESTIC ANIMALS

For external use on dogs ONLY.

DO NOT USE ON CATS – IF INGESTED BY CAT THAT ACTIVELY GROOMS A RECENTLY TREATED DOG, THIS PRODUCT MAY HAVE SERIOUS HARMFUL EFFECTS. IF THIS OCCURS, CONTACT YOUR VETERINARIAN IMMEDIATELY.

Do not use on dogs under 12 weeks of age. Individual sensitivities, while rare, may occur after using ANY pesticide product. Dogs may experience some temporary irritation at the site of product application. If signs of sensitivity occur, bathe your pet with mild soap or shampoo and rinse with large amounts of water. If signs of sensitivity occur and persist, contact a veterinarian immediately. If your dog has an unusual reaction to the initial application, consult a veterinarian before repeating application. Certain medications can interact with pesticides. Consult a veterinarian before using on medicated, debilitated, aged, pregnant or nursing dogs, or animals known to be sensitive to pesticide products.

FIRST AID	
IF SWALLOWED:	• Call a poison control center or doctor immediately for treatment advice. • Have person sip a glass of water if able to swallow. • Do not induce vomiting unless told to do so by a poison control center or doctor. • Do not give anything to an unconscious person.
IF IN EYES:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
IF ON SKIN OR CLOTHING :	• Take off contaminated clothing. • Rinse skin immediately with plenty of water for t5-20 minutes. • Call a poison control center or doctor for treatment advice.
Have product container or label with you when calling a poison control center or doctor, or going for treatment. **You may also contact the Hotline number 1-800-338-3659 for human or veterinary health concerns, emergency medical treatment information or pesticide incidents.**	

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in any manner inconsistent with its labelling. Do not allow children to apply product. TO PREVENT HARM TO YOU AND YOUR DOG, READ ENTIRE LABEL AND DIRECTIONS BEFORE EACH USE. FOLLOW ALL DIRECTIONS AND PRECAUTIONARY STATEMENTS CAREFULLY. FOR EXTERNAL USE ON DOGS ONLY. DO NOT USE ON CATS OR RABBITS. DO NOT USE ON OTHER ANIMALS.

DO NOT USE DN CATS.

FOR EXTERNAL USE ON DOGS ONLY. Do not use on dogs under 12 weeks of age. —Do not split tubes between dogs. Do not use multiple tubes on one dog. Weigh your dog to be sure you are applying the right dose formulated for the weight of your dog. Overdosing your dog can result in serious illness. Do not bathe your dog within the first 24 hours after the product has been applied. If your dog is exhibiting signs of and/or is being treated for skin problems, talk to your veterinarian before applying any topical flea and tick control product.

Do not apply more often than once a (per) month (every 30 days).

For use in DOGS (t2 weeks old or older). To repel and kill fleas, ticks, and mosquitoes; to kill lice and to aids in control of mites; to repel and prevent blood feeding by biting flies. Apply monthly according to directions.

APPLICATION DIRECTIONS

t. Remove one applicator from packaging.
Hold applicator upright and remove cap.

2. Invert cap and place other end back onto applicator tip.
Push cap down to break seal.
Remove cap prior to treatment application.

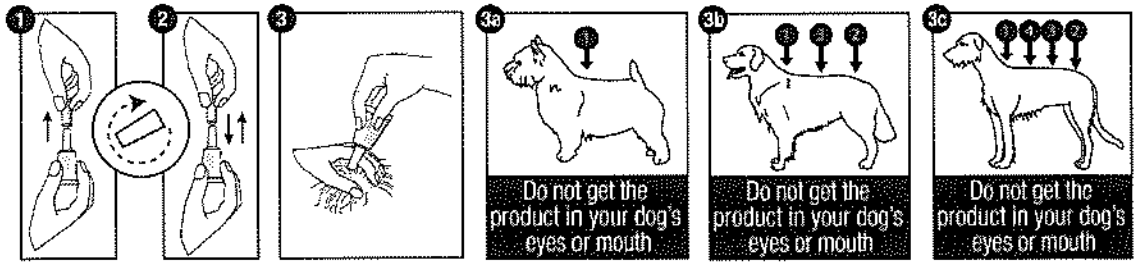
3. Part dog's hair until skin is visible.
Place applicator tip directly against exposed skin.

3a. For **small dogs (12 weeks old or older) and weighing up to 22.9 lbs**- Deposit entire contents by squeezing the entire applicator contents onto dog's skin, at a single site, between the shoulder blades as shown in diagram 3a.

3b. For **medium dogs 23-44.9 lbs or large dogs 45-88.9 lbs**- Apply the product evenly to three spots on the dog's back, starting between the shoulder blades and continuing on to the second and third spots as shown in diagram 3b, squeezing the applicator until empty.

3c. **For extra large dogs 89-132 lbs**- Apply the product evenly to four spots on the dog's back, starting between the shoulder blades and continuing on to the second, third and fourth spots as shown in diagram 3c, squeezing the applicator until empty.

Ensure that EFFITIX™ Topical Solution for Dogs is not applied superficially on dog's hair.



FREQUENCY OF APPLICATION

Fleas, ticks, (biting and chewing) lice infestations ~~and mite infestations~~ can be controlled with monthly applications of EFFITIX™ Topical Solution for Dogs. Biting flies and mosquitoes are (also) repelled by EFFITIX™ Topical Solution for Dogs.

Fleas: EFFITIX™ Topical Solution for Dogs can start killing adult fleas within 6 hours and lasts for (up to) a month. Apply monthly if your dog has fleas that may cause flea allergy dermatitis (FAD), or if re-infestation is likely.
Ticks: EFFITIX™ Topical Solution for Dogs can kill ticks for (up to) a month. Apply monthly where tick control is consistently needed.
Lice: EFFITIX™ Topical Solution for Dogs can kill biting and chewing lice for (up to) a month. Apply monthly where lice control is consistently needed.
Mites: EFFITIX™ Topical Solution for Dogs aids in (the) control of (sarcoptic mange)/(mite infestations that may cause sarcoptic mange).
Biting flies and Mosquitoes: When applied monthly, EFFITIX™ Topical Solution for Dogs (prevents blood feeding by) (and) (repels) biting flies and mosquitoes for up to 4 weeks (a [one] month). Kills mosquitoes for up to four weeks (a [one] month).

Notes: Wait at least 30 days before re-application of EFFITIX™ Topical Solution for Dogs. Avoid contact with treated area until dry.

STORAGE AND DISPOSAL

Do not contaminate water, food, or feed by storage and disposal.

STORAGE: Store unused product in original container only, out of reach of children and animals.

PESTICIDE /CONTAINER DISPOSAL: If empty: Nonrefillable. Do not reuse or refill this container. Offer for recycling, if available. **If partially filled:** Call your local solid waste agency for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND DISCLAIMER

VIRBAC warrants this product only if it is used, stored and handled in accordance with the label instructions. The buyers and users are solely responsible for all risks of use and handling of this product when such use and handling are contrary to or differ from the label instructions. To the extent permitted by applicable law, any damages arising from a breach of this warranty shall be limited to direct damages only and shall not include any type of consequential damages.

How supplied: For easy and convenient application, EFFITIX™ Topical Solution for Dogs is available in sizes for small dogs 12 weeks old or older up to 22.9 lbs (0.034 fl oz)/(t.0 mL), medium dogs 23-44.9 lbs (0.068 fl oz)/(2.0 mL), large dogs 45-88.9 lbs (0.135 fl oz)/(4.0 mL), and extra large dogs 89-132 lbs (0.203 fl oz)/(6.0 mL).

Net Contents: t (3, 6 or 36) single-dose applicator(s) per package containing 1mL (2mL, 4mL or 6mL)/ 0.034 fl oz (0.068 fl oz, 0.135 fl oz, 0.203 fl oz) (of solution).

(Detachable) calendar (monthly application) reminder stickers (with illustration of dog or puppy)

EPA Reg. No. 2382-RIT
EPA Est. No. 2382-FRA-1

VIRBAC AH, INC.
PO BOX 162059
FORT WORTH TX 76161
1-800-338-3659

Made in France
EFFITIX™ is a trademark of Virbac S.A.
Questions or comments?
Call: 1-800-338-3659

{Text for Front Panel, Back Panel, Inside Flap and Side Panel}

See package insert(s) for directions for use and frequency of application
See package insert for directions for use and storage and disposal
See package insert for frequency of application and storage and disposal
Open resealable label for directions for use
Open resealable label for directions for use and storage and disposal
See back panel for additional precautionary statements
See package insert(s) for frequency of application
See enclosed insert(s) for directions for use and storage and disposal
See enclosed insert(s) for directions for use
Lift here to open (LIFT HERE TO OPEN)
For Use on Dogs ONLY
Use ONLY on dogs
See inside flap for directions for use

{Text for Foil of Blister package}

Virbac
EFFITIX™ Topical Solution For Dogs
Only for use on dogs up to 22.9 lbs (23-44.9 lbs, 45-88.9 lbs, 89- 132 lbs)/0.034 fl oz (0.068 fl oz, 0. t35 fl oz, 0.203 fl oz) (1.0 mL, 2.0 mL, 4.0 mL, 6.0mL)
Contains fipronil (6.01%) and permethrin (44.88%)
KEEP OUT OF REACH OF CHILOREN
CAUTION
See full label for additional directions
EPA Reg. No. 2382-XXX
DO NOT USE ON CATS
CAT PROHIBITION ICON

{Text for Applicator Tube}

Virbac
EFFITIX™
Topical Solution For Dogs
Only for use on dogs
up to 22.9 lbs (23-44.9 lbs, 45-88.9 lbs, 89-132 lbs)
0.034 fl oz (0.068 fl oz, 0. t35 fl oz, 0.203 fl oz) [/ t.0 mL (2.0 mL, 4.0 mL, 6.0mL)]
Contains fipronil (6.01%)
and permethrin (44.88%)
KEEP OUT OF REACH OF CHILOREN
CAUTION
See full label for additional directions
DO NOT USE ON CATS
EPA Reg. No. 2382-XXX
CAT PROHIBITION ICON

MARKETING CLAIMS

[Multiple infestations]

- For convenient, quick-acting, long-lasting~~, effective~~ control of fleas, ticks, mosquitoes and ~~, lice and mites~~.
- (When) Applied topically on a monthly basis, EFFITIX™ Topical Solution for Dogs repels and kills fleas, ticks and mosquitoes, kills (biting, chewing) lice, aids in control of mites~~, ,~~and repels (and inhibits blood feeding) by biting flies and mosquitoes.
- ~~(When) Applied topically on a monthly basis, EFFITIX™ Topical Solution for Dogs repels and kills fleas, ticks and mosquitoes, kills (biting, chewing) lice, aids in control of mites, and repels and inhibits blood feeding by biting flies and mosquitoes.~~
- For easy and convenient application, EFFITIX™ Topical Solution for Dogs is available in sizes for small dogs (12 weeks old or older) and up to 22.9 lbs (0.034 fl oz)(t.0 mL), medium dogs 23-44.9 lbs (0.068 fl oz) (2.0mL), large dogs 45-88.9 lbs (0.135 fl oz) (4.0 mL), and extra large dogs 89-132 lbs (0.203 fl oz) (6.0 mL).
- EFFITIX™ Topical Solution for Dogs contains the active ingredients fipronil and permethrin, which control infestations caused by fleas, ticks and ~~, lice, and mites~~; repel (against) biting flies, and repel and kill mosquitoes.
- Kills fleas, ticks, lice, and mosquitoes, repels biting flies and mosquitoes
- Repels and kills fleas and ticks
- Repels fleas, ticks, biting flies and mosquitoes
- Kills, repels and detaches ticks
- ~~Kills lice and aids in control of mites~~
- For the control and prevention of flea]and lice] infestations
- Flea, tick, (biting and chewing) ~~lice and mite~~ lice infestations~~,~~ can be controlled with monthly applications of EFFITIX™ Topical Solution for Dogs. Biting flies and mosquitoes are (also) repelled by EFFITIX™ Topical Solution for Dogs.
- ~~Controls highly [irritating] [annoying] [flea] bites~~
- ~~Effective M~~monthly application against fleas, ticks and mosquitoes
- Kills fleas, ticks and mosquitoes for (up to) one month
- Monthly application is recommended for control and prevention of fleas, ticks and mosquitoes
- Long lasting flea, tick and mosquito control for your pet
- EFFITIX™ Topical Solution for Dogs is indicated for the prevention and control of fleas, ticks, mosquitoes, and lice on dogs ~~8~~ 12 weeks of age and older
- Helps to relieve your dog's pain (discomfort) by controlling flea, tick~~, mite~~ and lice infestations
- Kills the vectors that may transmit Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, hepatozoonosis and heartworm disease.
- Kills fleas, ticks, mosquitoes, lice, and aids in control of mites
- Kills and repels fleas, ticks, and mosquitoes.
- ~~(Also) kills lice, and aids in the control of mites.~~

[Fleas]

- Fleas: EFFITIX™ Topical Solution for Dogs can kill adult fleas in 6 hours (and lasts) for (up to) one (a] month. Apply monthly if your dog has fleas that may cause flea allergy dermatitis (FAD), or if reinfestation is likely.
- Kills newly emerged adult fleas prior to egg laying
- Kills fleas (within 6 hours) that may transmit bartonellosis, (tularemia) (and tapeworm)
- Kills fleas (within 6 hours) that may transmit diseases, including bartonellosis, (tularemia) (and tapeworm infestations)
- Kills fleas (within 6 hours) that may transmit diseases, including bartonellosis and tularemia
- Rapid kill of fleas is important in the prevention of disease transmission by (these) parasites
- Acts to kill fleas that may transmit disease, such as bartonellosis and tularemia
- Kills fleas that may serve as an intermediate host for tapeworms (*Dipylidium caninum*)
- Kills fleas that may serve as an intermediate host for cysticercoids of tapeworms
- Kills fleas that may serve as hosts for life cycle intermediates of tapeworms
- Kills (adult) fleas (within 6 hours) that may cause Flea Allergy Dermatitis (FAD) (or) (flea-bite anemia)
- Fleas do not have to bite to die
- Controls highly]irritating] [annoying] [flea] bites
- EFFITIX™ Topical Solution for Dogs rapidly kills fleas that may cause FAD (Flea Allergy Dermatitis)
- The successive feeding activity of fleas on dogs may elicit a hypersensitivity skin disorder known as Flea Allergy Dermatitis (FAD)
- EFFITIX™ Topical Solution for Dogs kills fleas and may reduce the incidence of Flea Allergy Dermatitis (FAD)
- Kills adult fleas for up to one month (4 weeks)
- Kills fleas
- Easy to apply, control of (for) fleas that lasts up to 1 month (4 weeks)
- EFFITIX™ Topical Solution for Dogs kills fleas on your dog
- Once a month topical flea control for dogs t28 weeks of age or older
- EFFITIX™ Topical Solution for Dogs is indicated for the prevention and control of fleas on dogs 12 weeks of age and older
- One application prevents further flea infestations for up to (4 weeks) (a [one] month]
- Monthly treatment (all year) is recommended for control and prevention of fleas
- ~~Regular (monthly) use breaks the flea life cycle~~
- Provides ongoing protection against fleas and the diseases they may transmit for one month
- Stops existing flea infestations by rapidly killing adult fleas
- Kills fleas before they lay eggs
- Stops existing flea infestations by killing adult fleas
- Prevents]Stops] re-infestations by killing adult fleas (before they lay eggs)
- Treatment with EFFITIX™ rapidly kills fleas which may cause flea allergic dermatitis]FAD] or flea bite hypersensitivity
- Controls flea problems
- Provides flea protection
- Use flea [prevention]]protection] year-round
- EFFITIX™ Topical Solution for Dogs controls flea infestation that may lead to painful skin irritation and bacterial infection

[Ticks]

- Ticks: EFFITIX™ Topical Solution for Dogs can kill ticks for ~~at least a~~(up to) a]one] month. Apply monthly where tick control is consistently needed.
- Kills and repels all stages of Brown dog ticks, American dog ticks, Lone Star ticks, and Deer ticks (that may transmit Lyme disease, Rocky Mountain Spotted Fever, babesiosis, ehrlichiosis and anaplasmosis)
- Kills ticks including Deer ticks (that may transmit Lyme disease), American dog ticks (that may transmit Rocky Mountain Spotted Fever), Brown dog ticks (that may transmit ehrlichiosis), and Lone Star ticks (that may transmit hepatozoonosis) for up to one month (4 weeks)
- Kills ticks including Deer ticks (that may transmit Lyme disease), American dog ticks (that may transmit Rocky Mountain Spotted Fever], and Brown dog ticks (that may transmit ehrlichiosis) for up to one month (4 weeks).
- Kills Brown dog ticks (*Rhipicephalus* spp), American dog ticks (*Dermacentor variabilis*), Deer ticks (*Ixodes* spp) and Lone Star ticks (*Amblyomma americanum*) for up to one month (4 weeks).
- Kills *Amblyomma americanum* (Lone Star ticks) for 4 weeks (for up to one month).
- ~~M~~Effective monthly application against ticks

[Mosquitoes and biting flies]

- Kills mosquitoes
- Kills mosquitoes for up to 28 days (four weeks) (a]one) month)
- Repels and inhibits blood feeding by biting flies and mosquitoes
- Biting flies and mosquitoes: When applied monthly, EFFITIX™ Topical Solution for Dogs (prevents blood feeding by) (and) (repels] biting flies and mosquitoes for (up to) 4 weeks (a [one] month)
- Repels and kills mosquitoes for up to four (4) weeks
- Prevents blood feeding by mosquitoes
- Repels and prevents (inhibits) blood-feeding by biting flies
- Repels and kills mosquitoes often before they have a chance to take a blood meal
- [(Prevents blood-feeding by) (Kills and repels)] mosquitoes
- Repels biting flies
- ~~Repels and inhibits blood-feeding by biting flies~~
- Repels [(annoying)(bothersome)(nuisance)] biting flies
- Inhibits [(annoying)(bothersome)(nuisance)) biting flies
- ((Prevents)(inhibits)] blood-feeding by biting flies
- Kills mosquitoes that may carry heartworm disease
- Repels and kills mosquitos (*Culex spp, Ochlerotatus* spp, *Aedes spp*) which may vector heartworm (*Dirofilaria immitis*) for one month

[Lice and Mites]

- Lice: EFFITIX™ Topical Solution for Dogs can kill biting and chewing lice for ~~(~~up to) a |one| month ~~or longer~~. Apply monthly where lice control is consistently needed.
- Mites: ~~(When applied monthly,~~ EFFITIX™ Topical Solution for Dogs) aids in (the) control of mites (that may cause sarcoptic mange)

- EFFITIX™ Topical Solution for Dogs aids in (the) control of mite infestations (that may cause sarcoptic mange).
- (When applied monthly,) EFFITIX™ Topical Solution for Dogs aids in (the) control of sarcoptic mange.

~~•When applied monthly, EFFITIX™ Topical Solution for Dogs aids in the control of sarcoptic mange (mite).~~
~~•Aids in the control of mites (that may cause sarcoptic mange)~~

- Aids in (the) control of sarcoptic mange mite infestation
- Kills chewing and ~~,~~ biting ~~and~~ lice
- (Also) Kills lice and aids in control of mites

- Controls existing chewing/biting lice infestations
- Kills |(biting) (chewing)) lice
- For control and prevention of |(biting) (chewing)| lice (infestations)
- Stops existing [(biting) |chewing)) lice infestations
- Prevents and controls [(biting) (chewing)] lice (infestations)
- Provides ~~effective~~ control of [(biting) (chewing) | lice (infestations)
- Kills |(biting) (chewing)) lice and prevents further infestations
- For control and prevention of (infestations with) |(biting) (chewing)| lice

[Others]

- 1 (3, 6, 36) applicator(s| (tube|s|) 1.0 mL (2.0 mL, 4.0 mL, 6.0 mL)
- 1 (3, 6, 36) applicator(s) (tube[s]) 0.034 fl oz (0.068 fl oz, 0.135 fl oz, 0.203 fl oz)
- 1 (3, 6, 36) applicator(s| (tube|s)) 0.034 fl oz [f.0 mL| (0.068 fl oz |2.0 mL), 0.135 fl oz |4.0 mL|, 0.203 fl oz (6.0 mL|)
- 1 (3, 6, 36) applicator(s) (tube[s)) (each) containing 0.034 fl oz [1.0 mL[(0.068 fl oz |2.0 mL), 0.135 fl oz |4.0 mL|, 0.203 fl oz |6.0 mL|)
- 1 (3, 6, 36) applicator(s) (tube[s))
- 1 (3, 6, 36) monthly dose(s) (application|s|)
- f (3, 6, 36) applicator(s) (tube[s)) 1 (3, 6, 36) month(ly) dose(s) (application(s)
- DO NOT USE ON CATS
- This product is only for use on dogs 12 weeks of age or older up to 22.9 lbs (weighing 23 to 44.9 lbs, weighing 45 to 88.9 lbs, weighing 89 to 132 lbs)
- Up to 22.9 lbs (weighing 23 to 44.9 lbs, weighing 45 to 88.9 lbs, weighing 89 to 132 lbs)
- Easy and convenient application (applications)
- Remains effective for a (one) month (4 weeks)
- Stops existing infestations and prevents establishment of new infestations
- Reinfestation of fleas, ticks and mosquitoes, ~~(~~biting, chewing) lice ~~and mites,~~ and biting flies is prevented for a (one) month or longer
- Convenient topical treatment for dogs
- Quick onset of activity
- Persistent efficacy through 30 days
- Prevents (re-)infestation for one month
- Once monthly application
- Quick drying, non-greasy
- (Convenient) (to use) Easy (to apply) spot-on (topical) application
- Fragrance (odor) free
- No noticeable odors
- Single application lasts 4 weeks (one month) (30 days)
- Easy to use applicator makes treatment simple (trouble free, smooth) and comfortable for your pet
- Convenient, easy to apply topical solution
- Convenient, easy to apply and fragrance free topical solution
- Starts working by (on) contact
- (In) child-resistant packaging
- Convenient (to use), easy to apply (topical solution)
- EFFITIX™ Topical Solution for Dogs remains effective after bathing, shampooing, water immersion, or sunlight exposure.
- Waterproof (remains effective after bathing and swimming) for up to four weeks (a month) (one month)
- Remains effective after exposure to sunlight
- Remains effective even after bathing, water immersion, or exposure to rain or sunlight
- Remains effective even after bathing (and swimming)
- Remains effective after exposure to rain and/or sunlight
- Still works after bathing, swimming or exposure to sunlight
- Maintains residual efficacy after bathing and swimming
- Remains effective after bathing (and swimming) [(for a month) (for one month) (for up to four weeks)|
- For dogs that enjoy the outdoors
- For indoor and outdoor dogs
- Convenient topical treatment for dogs who enjoy the outdoors
- Formulated for dogs that love the outdoors
- For dogs that enjoy the outdoors

- Available from licensed veterinarians
- ~~Sold by veterinarians~~
- ~~Veterinarian recommended~~
- Illustration of flea life cycle
- Illustration of tick life cycle
- Illustration of mosquito life cycle
- Illustration of mite life cycle
- Illustration of louse life cycle
- Illustration of flea
- Illustration of tick
- Illustration of mosquito
- Illustration of mite
- Illustration of louse
- Picture or illustration of a dog (or puppy)
- Picture or illustration of the Virbac logo
- Picture or illustration of the primary package (applicator tubes)
-

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM:

To: Bonaventure Akinlosotu

From: Clayton Myers, Entomologist **Date:** November 8, 2011

11-8-11

Subject: PRODUCT PERFORMANCE DATA EVALUATION RECORD

DP barcode:	391921
Decision no.:	448350
Submission no:	897940
Action code:	R310
Product Name:	Effitix Topical Solution for Dogs
EPA Reg. No or File Symbol:	2382-RIT
Formulation Type:	Pet Spot-On

Ingredients statement from the label with PC codes included: Permethrin, 44.88% PC: 109701; Fipronil, 6.01% PC: 129121

Application rate(s) of product and each active ingredient (lbs. or gallons/1000 square feet or per acre as appropriate; and g/m^2 or mg/cm^2 as appropriate): Rate not provided on label. States one bottle (sizes not listed in net contents) will treat a surface up to [360][500] square feet.

I. Action Requested: Data was submitted to support pest claims for a pet spot-on product.

II. Background: The registrant seeks to register a fipronil/permethrin combo spot-on product for control of fleas, ticks, and other pests on dogs. The registrant has submitted 9 studies to support efficacy claims, in addition to selective citations.

III. MRID Summaries: (Primary Review attached)

a. MRID 48510701: Efficacy Study Against Fleas (Ctenocephalides) on Dogs: Onset of Action.

1. GLP Study
2. A laboratory study was conducted to test the speed of effectiveness of a fipronil/permethrin combination product with equivalent concentrations as the submitted product (on a w/w % basis). Dogs were qualified for flea retention and allocated into 2 groups, a treatment and a control group (10 dogs each in the treated groups and 6 in the control group). Dogs were infested with fleas on day -6 and day -1. After treatment on day 0, dogs were kept in individual pens. Flea comb counts were conducted on day -5 and on day 0 at 2, 6, and 12 hours after treatment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Mean flea reduction efficacy at 6 hours after treatment was 94.4% (88.6% if the regular arithmetic mean was used). Flea efficacy exceeded 99% by 12 hours after treatment.
4. The primary reviewer agrees that the study is adequate to support killing claims against fleas within 6 hours of treatment. The reviewer comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the

concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and claims of killing fleas within 6 hours of treatment are adequately supported.

b. MRID 48467122: Efficacy Study Against Rhipicephalus sanguineus in Dogs: Duration of Action.

1. GLP Study
2. A laboratory study was conducted to test the efficacy and duration of control of Brown Dog Ticks on dogs for a fipronil/permethrin combination product with equivalent concentrations as the submitted product on a w/w % basis). Dogs were infested with adult ticks for the study. 6 dogs were placed in a treatment group and 6 others in a control group. Each dog received 50 ticks on day -6, and days 0, 7, 14, 21, 28, 35, 42, 29, 56, and 63. Tick counts and mortality assessment was conducted on day -4, 1, 2, 9, 16, 23, 30, 37, 44, 51, 58, and 65. The ticks were categorized as being alive or dead, and also in 3 subgroups: free, attached and unengorged, or attached and engorged. Ticks were counted and removed during the 48 h assessment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Efficacy at 2 days after treatment was 86.6%, but efficacy then exceeded 90% after each subsequent reinfestation through day 51. The study author states that efficacy should be adequately supported for 7 weeks after treatment.
4. The primary reviewer agrees that the study is adequate to support claims against BDT through 7 weeks after treatment. The reviewer comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and claims of killing BDT are supported for 7 weeks after treatment.

c. MRID 48467123: Efficacy Study Against Dermacentor variabilis on Dogs: Duration of Action.

1. GLP Study
2. A laboratory study was conducted to test the efficacy and duration of control of American Dog Ticks on dogs for a fipronil/permethrin combination product with equivalent concentrations as the submitted product on a w/w % basis). Dogs were infested with adult ticks for the study. 6 dogs were placed in a treatment group and 6 others in a control group. Each dog received 50 ticks on day -6, and days 0, 7, 14, 21, 28, 35, 42, 29, 56, and 63. Tick counts and mortality assessment was conducted on day -4, 1, 2, 9, 16, 23, 30, 37, 44, 51, 58, and 65. The ticks were categorized as being alive or dead, and also in 3 subgroups: free, attached and unengorged, or attached and engorged. Ticks were counted and removed during the 48 h assessment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Efficacy at 2 days after treatment was 49.4%, but efficacy then exceeded 90% after each subsequent reinfestation through day 44. The study author states that efficacy should be adequately supported for 6 weeks after treatment.
4. The primary reviewer agrees that the study is adequate to support claims against ADT through 6 weeks after treatment. The reviewer comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and claims of killing ADT are supported for 6 weeks after treatment.

d. MRID 48467124: Efficacy Study Against the Brown Dog Tick (Rhipicephalus sanguineus) and the Cat Flea (Ctenocehpalides felis) on Dogs: Effects of Shampooing and Periodic Water Immersions.

1. GLP Study
2. A laboratory study was conducted to to evaluate the efficacy and duration of control of a fipronil/permethrin combination product against fleas and ticks after shampooing and water immersion, in support of waterproof claims. 24 dogs were blocked within gender and weight groups in 6 blocks of 4 dogs in descending order of pre-treatment flea counts, and assigned to 3 treatment groups: Group 1 was a control group that was shampooed and water immersed, 6 dogs. Group 2 was treated with the test

substance, 6 dogs. Group 3 was treated with the test substance and shampooed, 6 dogs. Group 4 was treated with the test substance and water immersed, 6 dogs. Dogs were infested with fleas (100) on days -4, 0, 7, 14, 21, and 28. Dogs were also infested with ticks (50) on days -5, -1, 6, 13, 20, and 27. Shampooing occurred on day 12. Water immersion on days 12 and 26. Flea and Tick counts were conducted on days -2, 2, 9, 16, 23, and 30. For water immersion and shampooing, animals were rinsed using a shower head for 5 minutes at a flow rate of 2 gallons/minute. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Tick efficacy at 2 days was variable, but at days 9-30, tick efficacy exceeded 99% for all treatment groups, including dogs that were shampooed or water immersed. Flea efficacy exceeded 90% at 2 days, and was at 100% at days 9-10, for all treatment groups, including dogs that were shampooed or water immersed. The study author states that efficacy is adequately supported for fleas and ticks after water immersion and shampooing.
4. The primary reviewer agrees that the study is adequate to support claims against ticks and fleas through 1 month after treatment, with shampooing and water immersion. The reviewer comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and claims of fleas and ticks for 1 month after treatment, with water immersion and shampooing, i.e., 'waterproof' claims.

e. MRID 48467125: The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%, Permethrin 50%) Compared to a No Treatment Control Against Artificially Induced Infestations of Ticks (Amblyoma americanum) on Dogs.

1. GLP Study
2. A laboratory study was conducted to test the efficacy and duration of control of Amblyoma americanum on dogs for a fipronil/permethrin combination product with equivalent concentrations as the submitted product on a w/w % basis). Dogs were infested with adult ticks for the study. 6 dogs were placed in a treatment group and 6 others in a control group. Each dog received 50 ticks on day -7, and days 0, 7, 14, 21, 28, 35, and 42. Tick counts and mortality assessment was conducted on day -4, 1, 2, 9, 16, 23, 30, 37, and 44. The ticks were categorized as being alive or dead, and also in 3 subgroups: free, attached and unengorged, or attached and engorged. Ticks were counted and removed during the 48 h assessment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Efficacy at 2 days after treatment was 70%, but efficacy then exceeded 90% after each subsequent reinfestation through day 23. Efficacy was 88% at day 37. The study author states that efficacy should be adequately supported for 23 days after treatment, with some residual control of ticks through 30 and 37 days.
4. The primary reviewer agrees that the study is adequate to support claims against BDT through 3 weeks after treatment, but that one month control claims were not adequately supported, as the 90% efficacy threshold was not met for day 30. The reviewer also comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is unacceptable and claims of killing Amblyoma americana for one month, but is partially acceptable and is adequate to support claims for 3 weeks after treatment.

f. MRID 48467126: Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7% w/v, Permethrin 50% w/v) Compared to a No Treatment Control Against Artificially Induced Infestations of Ticks (Ixodes scapularis) on Dogs.

1. GLP Study
2. A laboratory study was conducted to test the efficacy and duration of control of Black Legged Ticks on dogs for a fipronil/permethrin combination product with equivalent concentrations as the submitted product on a w/w % basis). Dogs were infested with adult ticks for the study. 6 dogs were placed in a treatment group and 6 others in a control group. Each dog received 40 ticks on day -7, and with 50 ticks on days 0, 7, 14, 21, 28, 35, and 42, and with 35 ticks on day 49. Tick counts and mortality assessment was conducted

on day -5, 2, 9, 16, 23, 30, 37, 44 and 51, at 48 hours after infestation. The ticks were categorized as being alive or dead, and also in 3 subgroups: free, attached and unengorged, or attached and engorged. Ticks were counted and removed during the 48 h assessment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Efficacy at 2 days after treatment was 94%, and efficacy then exceeded 90% after each subsequent reinfestation through day 37. The study author states that efficacy should be adequately supported for 37 days after treatment, with some residual control of ticks through 44 and 51 days.
4. The primary reviewer agrees that the study is adequate to support claims against BLT through 30 days after treatment. The reviewer also comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and one month claims against BLT are adequately supported.

g. MRID 48467127: Determination of a Combination of Fipronil and Permethrin in Topical Solution Against Mosquitoes (*Aedes aegypti*) on Dogs.

1. GLP Study
2. A laboratory study was conducted to test the efficacy of a fipronil/permethrin product against mosquitoes for repellence (preventing feeding) and killing of A. aegypti. Dogs were qualified as mosquito hosts, with dogs allowing a feeding rate of 40% were considered acceptable for the study. 12 dogs were randomly assigned into 2 groups, a treatment and control group. The product was applied on day 0. Dogs were exposed for 28-35 minutes to unfed female mosquitoes in exposure cages on days 1, 7, 14, 21/22, 28, and 35-37. Dogs were sedated during infestations. Afterwards, the mosquitoes were collected and dogs were removed from the exposure cages and returned to normal housing. At 50-90 minutes after exposure, dead and alive mosquitoes were counted. The mosquitoes were frozen and crushed to determine if a blood meal had been taken. Mortality was calculated for both feeding efficacy (repellence) and killing efficacy. Efficacy calculations were made using Abbott's Formula.
3. Short-haired dogs were more susceptible to mosquitoes than long hair dogs. The test product has a more effective repellence efficacy than killing efficacy. Killing efficacy never exceeded 59.5%. Repellence efficacy was 91.7% efficacy at 7 days after treatment.
4. The primary reviewer concludes that the study is not acceptable to support claims against mosquitoes, as no killing efficacy was demonstrated and repellence was only adequate at 7 days after application. The study is not acceptable to support any claims against mosquitoes.

h. MRID 48467128: Repellence Efficacy Study of 104.05 Against Ticks (Dermacentor variabilis and Rhipicephalus sanguineus) on Dogs Under Laboratory Conditions.

1. GLP Study
2. A laboratory study was conducted to evaluate the repellence of ticks for a fipronil/permethrin combination product. 12 dogs were used in the study, with 6 dogs given treatment and 6 dogs left as an untreated control group. Adult BDT and ADT were used in artificial infestations. Dogs were infested with 30 unfed ticks on day -6 (R. sanguineus only), and days 1, 2, 7, 14, 21, 22, and 28. Tick assessments were conducted on days 1, 2, 7, 14, 21, 22, and 28 at 3 hours after infestation/reinfestation. Tick counts with removal were conducted on days -5, 2, 4, 8, 15, 22, 23, and 29, 24 hours after the infestations. Ticks were categorized as being alive or killed and in 3 subgroups: free, attached and engorged, or attached and unengorged. Ticks found in the infestation chamber after removal of the dogs were categorized as live, moribund or dead. % mortality was calculated using Abbott's Formula.
3. BDT repellence efficacy was 90-95% for the 3 hour assessments through 14 days. Efficacy was 99% or greater for the 24 hour assessment through 29 days. For ADT, repellence efficacy was 90-97% for the 3 hour assessments through 22 days. Efficacy was 97% or greater for the 24 hour assessment through 29 days. The author concludes that repellence efficacy for ticks is supported through up to 29 days after treatment.
4. The primary reviewer concurs that basic tick repellence claims are supported for up to one month after application. The study is acceptable to support claims of tick repellence for up to one month.

i. MRID 48467129: Summary of Efficacy Data for Effitix™ Topical Solution for Dogs End Use Product.

This MRID was a summary of selectively cited and submitted studies in support of label claims. The submission is supplemental.

j. Selective Citations of 60 MRIDs from the fipronil and permethrin efficacy database including the following:
43121114, 43121115, 43121116, 43121119, 43121120, 43121121, 43121122, 43444901, 43577701, 43577712, 43577713, 43951701, 44088901, 44942011, 44942106, 45618501, 45620502, 45620503, 45628104, 45628105, 45866901, 43577712, 43121114, 43121115, 43121117, 43121122, 43121118, 45620504, 45620505, 45620506, 43444901, 43444901, 43577701, 43951701, 45612701, 45620503, 45866901, 45620501, 45618101, 45628102, 45628103, 45628201, 45866902, 46019202, 46019201, 41038802, 41038803, 43137202, 43137203, 43396409, 43396410, 46006002, 41683903, 43111607, 43396409, 43396410, 46978901, 42256901, 43396409, 43396410

These studies support efficacy claims (in various versions) against fleas, ticks, lice (chewing/biting), mites (aids in control of sarcoptic mange), mosquitoes, and repellence of biting flies.

Claims are not supported for sand flies, for killing/control of mites (only 'aids in control'), or sucking lice.

IV. RECOMMENDATIONS:

(1) Labeling:

(a) What pests and site/pest combinations may be added as follows to the label based on the submitted ar cited data?

Fleas: Killing within 6 hours and control for up to one month. Also repellence of fleas.
Ticks: Killing and controlling for up to one month. Also repellence of fleas.
Mosquitoes: Killing and controlling for up to one month, also repellence and prevention of blood feeding for up to one month
Biting Flies: Repellence
Lice (chewing/biting): Killing and controlling for up to one month
Mites: Aids in control of sarcoptic mange/mites that may cause sarcoptic mange, etc.

(b) What pests and site/pest combinations must be removed from the label?

Any and all claims against sandflies
Any claims of control of fleas or ticks beyond one month (given that waterproof claims are included)
Killing/controlling claims against mites (only aids in control is supported)
Any and all claims against 'sucking' lice

(c) List changes to the directians for use:

None required

(d) List changes to the optional marketing claims:

The following marketing claims must be deleted from the label (pages 4-7)

All references to sandflies, killing/controlling of mites, and 'sucking' lice must be removed from all marketing claims and from the entire label. References to the word 'effective' are deemed inappropriate, as this implies a heightened comparative efficacy claim (a decision on the suitability of this claim is deferred to the product

manager). Finally, any and all claims of 'breaking the flea life cycle' must be deleted, as this product does not kill flea eggs or larvae. On a line-by-line basis, the claims marked with ~~strikethrough text~~ below must be deleted.

"For convenient, quick-acting, long-lasting ~~effective~~ control of fleas ticks . . ."

". . . (biting, chewing and ~~sucking~~) lice and ~~mites~~ . . ." All variations of these kill claims must be deleted throughout the label. Claims against mites may be expressed as 'aids in control.'

"Kills fleas, ticks, lice, ~~mites~~ and mosquitoes, repels biting flies and mosquitoes"

"Repels fleas, ticks, biting flies, ~~sandflies~~ and mosquitoes"

~~"Research has shown that flea, tick, (sucking, biting, and chewing) lice and mite infestations can be completely controlled with monthly applications of EFFITIX™ Topical Solution for Dogs."~~ The claim 'research has shown' is unacceptable and the claim 'can be completely controlled' implies 100% efficacy, which is also unacceptable.

~~"Effective~~ monthly application against fleas, ticks, and mosquitoes"

"Fleas: EFFITIX™ Topical solution for dogs can kill adult fleas in 6 hours ~~for up to three months~~. Apply monthly if your dog . . ."

"~~Effective~~ monthly application against fleas"

"~~Effective~~ monthly control of fleas"

"Easy to apply ~~(effective)~~ control . . ."

~~"Effectively breaks the flea life cycle"~~

~~"Effective~~ monthly application against ticks"

"Repels and inhibits blood feeding by biting flies, ~~sandflies~~ and mosquitoes" (delete all other references to sandflies)

"Lice: EFFITIX™ Topical Solution for Dogs can kill ~~sucking~~, biting and chewing lice for . . ." (delete all other references to sucking lice)

~~"Mites: When applied monthly, EFFITIX™ Topical Solution for Dogs kills mites"~~

~~"Mites (Cheyletiella yasguri): When applied monthly . . . ."~~

~~"Kills mites (that may cause sarcoptic mange)"~~ Can be revised to 'aids in control of mites that may cause . . ."

~~"Sold by veterinarians"~~

~~"Veterinarian recommended"~~

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 485107-01. Fourie, J.J. Efficacy Study Against Fleas (*Ctenocephalides felis*) on Dogs: Onset of Action. December 9, 2009.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: Dennis M Opresko
Date: OCT 19 2011

Secondary Reviewers:
Gene Burgess, Ph.D.

Signature: Gene Burgess, AE
Date: OCT 19 2011

Robert Ross, M.S., Program Manager

Signature: Robert H. Ross
Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: Jennifer Goldberg
Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**485107-01.** Efficacy Study Against Fleas (*Ctenocephalides felis*) on Dogs: Onset of Action. Fourie, J.J. 2009.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	VIRBAC SA
TESTING FACILITY:	ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	27/05/2009
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution

	PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.
PROPOSED LABEL MARKETING CLAIMS:	...can start killing adult fleas within 6 hr and lasts for up to three months.

STUDY REVIEW

Purpose: To test the speed of effectiveness of 104.05 spot-on formulation against *Ctenocephalides felis* fleas on dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa.

Test Material(s): 104.05 spot-on formulation (6.7% fipronil and 50% permethrin, w/vol).

Test Species Name, Life Stage, Sex and Age: Male and female adult dogs (*Canis familiaris*) greater than 6 months old.; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment and dewormed and did not harbor fleas at the initiation of the study. Dogs were separated by gender and ranked as follows: dogs weighing <18.14 kg were ranked first and then dogs weighing ≥18.14 kg were ranked in descending order of individual pre-treatment flea counts. Within each gender the dog weighing less than 18.14 kg with the highest pre-treatment flea count and the dog weighing ≥ 18.14 kg with the lowest pre-treatment count were allocated to Group 2 (treatment group). The remaining 12 dogs were blocked into 6 blocks of two animals each and within each block were randomly allocated to Group 1 (control) or Group 2. Laboratory breed strain (ClinVet – 2004, routinely fed on cats) of *Ctenocephalides felis* were used in the artificial infestations. Each dog was infested with 100 fleas on Day -6 and on Day -1. After treatment the dogs were kept in individual pens. Flea counts were conducted on Day -5 and on Day 0 (day of application) at 2, 6, and 12 hours after treatment.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One.

Number of individuals per replicate: Ten in the treated group; six in the negative control group.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 20±4°C; 12/12 light cycle.

Data or endpoints collected/recorded: Flea counts were conducted on Day -5 and on Day 0 (day of application) at 2, 6, and 12 hours after treatment.

Data analysis: Efficacy calculations were based on geometric means, and specifically on the geometric means of the flea data (count +1). One was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group. Percent efficacy was calculated as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live fleas on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live fleas on dogs in the treatment group (Group 2) at a specific time point.
Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on flea counts for the various assessment days were calculated and tabulated.

RESULTS

Raw data were not included in the study report. One protocol deviation was reported; two female dogs with the lowest pre-treatment flea count in the lower weight category (<18.14 kg) were excluded instead of the two female dogs with the lowest pre-treatment count per weight category because no female dog in the heavy weight category could be excluded. Flea counts for the negative control group and the treated group are shown in Table 1. Percent efficacy is shown in Table 2.

Table 1. Mean Flea Counts in the Control and Treated Groups.

Day, hr	Group 1, Negative Control		Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean
-5	67.5	67.0	75.3	73.7[a]
0, + 2 hr	71.5	71.3	55.4	48.1[a]
0, + 6 hr	71.0	70.9	8.1	4.0[b]
0, +12 hr	70.7	70.5	0.4	0.3[b]

[a]Not statistically significantly ($p > 0.05$) different from the control group on Day -5 and on Day 0, +2 hr.
[b]Statistically significantly ($p < 0.05$) different from the control group.

Table 2. Percent Efficacy Based on Geometric Means of Product 104.05 Against Fleas.

Day, hr	Group 2, Treated Group	
	Arithmetic Mean	Geomctric Mean
0, + 2 hr	22.5	32.5
0, + 6 hr	88.6	94.4
0, +12 hr	99.4	99.6

Study Author's Conclusions

The test product (104.05) killed >90% of the fleas on the treated dogs within 6 hr and >99% within 12 hr following administration.

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was met within 6 hr post administration. Note: the reported a.i. concentrations in the product tested (6.7% fipronil and 50% permethrin wt/vol) do not exactly match the label concentration (6.01% fipronil and 44.88% permethrin, presumably on a wt/wt basis). The concentrations of the active ingredients in the test product were not verified or supported by a Certificate of Analysis. The use of the geometric means in the data analysis was not adequately explained, although it could be argued that the results for each dog can be considered independent variables.

The study author stated that the application was one spot between the shoulder blades. The body weight of the study animals ranged between 10.2 kg (22.5 lb) and 20.2 kg (44.5 lb). On the label it is stated to apply the product evenly to three spots on the dog's back for medium (22-44.9 lb) or large dogs (45-88.9 lb).

Reviewer's Recommendations

Acceptable if the registrant can verify that the concentrations of the a.i. in the test product are the same as those on the label for "Effitix Topical Solution for Dogs" or are within the certified upper and lower limits of the product as specified on the CSF. Results support the label claim that the product starts killing fleas within 6 hr.

Note: The reported test concentrations (6.7% fipronil and 50% permethrin) were expressed on a wt/vol basis (p. 11 of 36 in MRID 485107-01). Other MRIDs in Task 2-30 30 (e.g., MRID 484671-26) indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-22. Fourie J.J. 104.05: Efficacy Study Against *Rhipicephalus sanguineus* in Dogs: Duration of Action. December 9, 2009.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: [signature]
Date: OCT 19 2011

Secondary Reviewers:
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Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: [signature]
Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-22.** 104.05: Efficacy Study Against *Rhipicephalus sanguineus* in Dogs: Duration of Action. Fourie, J.J. December 9, 2009.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau, Virbac SA
TESTING FACILITY:	ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa.
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	09/12/2009
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specificed by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided

FORMULATION TYPE: Topical solution

PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb
ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.

PROPOSED LABEL MARKETING CLAIM: ...can kill ticks for at least a month.

STUDY REVIEW

Purpose: To test the duration of action of 104.05 spot-on formulation against *Rhipicephalus sanguineus* ticks in dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa

Test Material(s): 104.05 spot-on formulation (6.7% fipronil and 50% permethrin).

Test Species Name, Life Stage, Sex and Age: Male and female adult dogs (*Canis familiaris*) older than 6 months old; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment; dewormed and "did not harbor ticks at the initiation of the study." Dogs were kept in individual pens 1.9 m by 2.97 m. Laboratory breed strain (French) of *Rhipicephalus sanguineus* were used in the artificial infestations. Immature ticks were fed on rabbits. Adult ticks at least one week old were used in the infestations (50% male and 50% female). Each dog received 50 unfed adult ticks on Day -6, Day 0 (2 hr ±15 min prior to treatment), and on Days +7, +14, +21, +28, +35, +42, +49, +56 and +63. After treatment, the dogs were kept in individual pens. Tick counts were conducted on Day -4, +1 (in situ), +2, +9, +16, +23, +30, +37, +44, +51, +58, and +65.

Treatments, including untreated control: 0.1 mL/kg

Number of replicates per treatment: One

Number of individuals per replicate: Six in the treated group and six in the control group.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: ~20 ± 4°C; 12/12 light cycle

Data or endpoints collected/recorded: Tick counts were conducted on Day -4, +1 (in situ), +2, +9, +16, +23, +30, +37, +44, +51, +58, and +65. The ticks were categorized as being alive or killed and in three subgroups: free, attached and unengorged, or attached and engorged (the latter category was not included during the 24 hr in situ count on Day 1. The ticks counted and removed during the 48 hr assessments were categorized according to gender. Dogs were sedated with medetomidine hydrochloride (1.0 mg/mL) to facilitate tick infestation.

Data analysis: Efficacy calculations were made for each treatment group at each assessment day. Efficacy was based on geometric means of the tick data (count +1). One was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group. Percent efficacy was calculated as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live ticks on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live ticks on dogs in the treatment group (Group 2) at a specific time point.

Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on tick counts for the various assessment days were calculated and tabulated.

RESULTS

Raw data sheets were included in the study report. No deviations from the study protocol were reported. Mean tick counts for the negative control group and the treated group are shown in Table 1. Percent efficacy is shown in Table 2. The immediate efficacy assessed after 24 hr was 47.1%; at 48 hr it was 86.6%. Greater than 90% efficacies were recorded up to 51 days post treatment with the exception of Day +37 when it was 87.3%.

Table 1. Mean Tick Counts in the Control and Treated Groups

Day	Group 1, Negative Control		Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean
-4	25.5	24.0	25.2	24.8
+1[a]	18.0	17.7	11.3	9.3[b]
+2	18.7	16.9	3.0	2.3[b]
+9	20.2	19.3	0.0	0.0[b]
+16	25.8	23.5	0.0	0.0[b]
+23	27.5	26.8	0.0	0.0[b]
+30	27.0	26.4	1.7	1.5[b]
+37	34.2	32.3	6.2	4.1[b]
+44	25.5	23.3	2.0	1.0[b]
+51	27.2	26.3	3.0	1.6[b]
+58	34.8	34.6	8.2	4.2[b]
+65	29.7	29.2	12.2	7.2[b]

[a]In situ counts
[b]Group 2 differed statistically significantly ($p < 0.05$) from Group 1.

Table 2. Percent Efficacy Based on Geometric Means of Product 104.05 Against Ticks

Day	Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean
+1[a]	37.0	47.1
+2	83.9	86.6
+9	100.0	100.0
+16	100.0	100.0
+23	100.0	100.0
+30	93.8	94.2
+37	82.0	87.3
+44	92.2	95.5
+51	89.0	94.0
+58	76.6	87.8
+65	59.0	75.2

[a]In situ counts

Study Author's Conclusions

A 7-week duration of action (>90%) was recorded against *Rhipicephalus sanguineus* ticks in dogs. No treatment related adverse effects occurred.

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was met. The reported a.i. concentrations in the test product (6.7% fipronil and 50% permethrin) do not exactly match the label concentration (6.01% fipronil and 44.88% permethrin). The concentrations of the active ingredients in the test product were not verified or supported by a Certificate of Analysis.

Reviewer's Recommendations

Acceptable if the registrant can verify that the concentrations of the a.i. in the test product are the same as those in "Effitix Topical Solution for Dogs" (see NOTE below). Results support the label claim that the product kills ticks for at least a month.

NOTE: Although not specifically stated in the study report, the reported test concentrations (6.7% fipronil and 50% permethrin) may have been based on weight per volume measurements. Other MRIDs in Task 2-30 indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-23. Fourie, J.J. 104.05: Efficacy Study Against *Dermacentor variabilis* on Dogs: Duration of Action. December 9, 2009.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

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Date: OCT 19 2011

Secondary Reviewers:
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Quality Assurance:
Jennifer Goldberg, B.S.

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Date: OCT 19 2011

Disclaimer

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DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-23.** 104.05: Efficacy Study Against *Dermacentor variabilis* on Dogs: Duration of Action. Fourie, J.J. December 9, 2009.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau,Virbac SA
TESTING FACILITY:	ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	09/12/2009
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution

PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb
ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.

PROPOSED LABEL MARKETING CLAIMS: ..can kill ticks for at least a month.

STUDY REVIEW

Purpose: To test the duration of action of 104.05 spot-on formulation against *Dermacentor variabilis* ticks on dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa.

Test Material(s): 104.05 spot-on formulation (6.7% fipronil and 50% permethrin).

Test Species Name, Life Stage, Sex and Age: Male and female adult dogs (*Canis familiaris*) greater than 6 months old; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment; dewormed and "did not harbor ticks." Dogs were kept in individual pens 1.9 m by 2.97 m. Dogs were separated by gender and blocked per gender in blocks of animals weighing <18.14 kg and animals weighing ≥18.14 kg in descending order of individual pre-treatment tick counts. Laboratory breed strain of *Dermacentor variabilis* were used in the artificial infestations. Immature ticks were fed on rabbits. Adult ticks at least one week old were used in the infestations (50% male and 50% female). Each dog received 50 unfed adult ticks on Day -6, Day 0 (2 hr prior to treatment), and on Days +7, +14, +21, +28, +35, +42, +49, +56 and +63. Tick counts were conducted on Day -4, +1 (in situ), +2, +9, +16, +23, +30, +37, +44, +51, +58, and +65.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One.

Number of individuals per replicate: Six treated and six controls.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: ~20±4°C; 12/12 light cycle; relative humidity 21.4-68.0% in room C of unit 20.

Data or endpoints collected/recorded: Tick counts were made on Day -4, +1 (in situ), +2, +9, +16, +23, +30, +37, +44, +51, +58, and +65. The ticks were categorized as being alive or killed and also in three subgroups: free, or attached and unengorged, or attached and engorged (the latter category was not included during the 24 hr in situ count on Day 0). The ticks counted and removed during the 48 hr assessments were categorized according to gender. Dogs were sedated with Domitor (1.0 mg medetomidine hydrochloride/mL) to facilitate tick infestation.

Data analysis: Efficacy calculations were made for each treatment group at each assessment day. Efficacy was based on geometric means of the tick data (count +1). One was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group. Percent efficacy was calculated as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live ticks on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live ticks on dogs in the treatment group (Group 2) at a specific time point.
Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on tick counts for the various assessment days were calculated and tabulated.

RESULTS

Data sheets with the individual animal results were included in the study report. Mean tick counts for the negative control group and the treated group are shown in Table 1. Percent efficacy is shown in Table 2. The immediate efficacy assessed after 24 hr was 0%; at 48 hr it was 49.4%. Efficacy values (based on geometric means) >90% were recorded from Day +9 to Day +44.

Table 1. Mean Tick Counts in the Control and Treated Groups

Day	Group 1, Negative Control		Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean
-4	27.3	26.3	28.7	27.2
+1[a]	15.5	14.8	25.3	24.4[b]
+2	19.2	15.5	11.7	7.9[b]
+9	26.2	20.3	0.0	0.0[b]
+16	23.8	21.5	0.0	0.0[b]
+23	28.7	24.9	0.2	0.1[b]
+30	23.7	19.8	0.2	0.1[b]
+37	26.0	23.4	2.0	1.4[b]
+44	17.5	14.6	1.8	0.8[b]
+51	13.3	10.9	4.0	2.0[b]
+58	20.0	18.7	5.5	4.4[b]
+65	14.0	12.0	3.5	3.0[b]

[a]In situ counts
[b]Group 2 differed statistically significantly ($p < 0.05$) from Group 1.

Table 2. Percent Efficacy Based on Geometric Means of Produet 104.05 Against Ticks

Day	Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean
+1[a]	0.0	0.0
+2	39.1	49.4
+9	100.0	100.0
+16	100.0	100.0
+23	99.4	99.5
+30	99.3	99.4
+37	92.3	94.0
+44	89.5	94.8
+51	70.0	81.3
+58	72.5	76.7
+65	75.0	74.8

[a]In situ counts

Study Author's Conclusions

Efficacy reached 100% at Day +9. A 6-week duration of action (>90%) was recorded against *Dermacentor variabilis* ticks in dogs. No treatment related adverse effects occurred.

Reviewer's Conclusions

Results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was reached at Day 9 post-treatment and lasted to Day +44. The reported a.i. concentrations in the test product (6.7% fipronil and 50% permethrin) do not exactly match the label concentrations (6.01% fipronil and 44.88% permethrin). The concentrations of the active ingredients in the test product were not verified or supported by a Certificate of Analysis.

Reviewer's Recommendations

Acceptable, if the registrant can verify that the concentrations of the a.i. in the test product are the same as those in "Effitix Topical Solution for Dogs" or are within the certified upper and lower limits of the product as specified on the CSF.

Note: Although not specifically stated in the study report, the reported test concentrations (6.7% fipronil and 50% permethrin) may have been based on weight per volume measurements. Other MRIDs in Task 2-30 30 (e.g., MRID 484671-26) indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, respectively, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-24. Fourie, J.J. Efficacy Study Against the Brown Dog Tick (*Rhipicephalus sanguineus*) and the Cat Flea *(Ctenocephalides felis)* on Dogs: Effects of Shampooing and Periodic Water Immersions. December 9, 2009.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

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Date: OCT 19 2011

Secondary Reviewers:
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Robert Ross, M.S., Program Manager

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Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

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Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**MRID: 484671-24.** Efficacy Study Against the Brown Dog Tick (*Rhipicephalus sanguineus)* and the cat Flea *(Ctenocephalides felis*) on Dogs: Effects of Shampooing and Periodic Water Immersions. Fourie, J.J. December 9, 2009.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau, Virbac SA
TESTING FACILITY:	ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	09/12/2009
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26^{lh}, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution

	PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.
PROPOSED LABEL MARKETING CLAIMS:	..can kill ticks for at least a month....can start killing adult fleas within 6 hr and lasts for up to three months.

STUDY REVIEW

Purpose: To test the effects of shampooing and periodic water immersion on the efficacy of formulation 104.05 against the brown dog tick (*Rhipicephalus sanguineus)* and the cat flea *(Ctenocephalides felis*) on dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa.

Test Material(s): 104.05 topical spot-on formulation (6.7% fipronil and 50% permethrin).

Test Species Name, Life Stage, Sex and Age: Male and female adult dogs (*Canis familiaris*) greater than 6 months old; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment; dewormed and did not harbor ticks at the initiation of the study. The 24 dogs used in the study were blocked within gender and weight groups (dogs weighing <18.14 kg and dogs weighing ≥18.14 kg) in six subsequent blocks of four dogs each in descending order of individual pre-treatment flea counts. Study groups were assigned to the blocks using randomization through minimization. The block which was not gender balanced was allocated to the control group. The remaining three groups were randomly assigned to the three treatment groups. Group #1 was the negative control (shampooed and water immersed, n=6). Group #2 was treated with the test substance (n = 6). Group #3 was treated with the test substance and shampooed (n = 6). Group #4 was treated with the test substance and water immersed (n = 6). After treatment on Day 0, the dogs were kept in individual pens (1.9 m x 2.97 m). Dogs were infested with 100 fleas on Days -4, 0 (4 hr prior to treatment); +7, +14, +21 and +28. Dogs were also infested with 50 ticks on Days -5, -1, +6, +13, +20, and +27. Shampooing occurred on Day +12; water immersion on Days +12 and +26. Tick and flea counts were conducted on Days -2, +2, +9, +16, +23, and +30. Ticks were categorized as alive or killed, as free or attached, and as engorged or unengorged.

Treatments, including untreated control: 0.1 mL for dogs weighing 2 to 10 kg; 2 mL for dogs weighing >10 kg up to 20 kg; 4 mL for dogs weighing >20 kg up to 40 kg.

Number of replicates per treatment: One per treatment type and one control group.

Number of individuals per replicate: Six.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 20±4°C; 12/12 light cycle

Data or endpoints collected/recorded: Tick and flea counts were conducted on Days -2, +2, +9, +16, +23, and +30. Ticks were categorized as alive or killed, as free or attached, and as engorged or unengorged.

Data analysis: Efficacy calculations were based on geometric means of the tick or flea data (count +1). "One" was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group. Percent efficacy was calculated as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live fleas (or ticks) on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live fleas (or ticks) on dogs in the treatment groups (Groups 2, 3 and 4) at a specific time point.

Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on tick and flea counts for the various assessment days were calculated and tabulated. The groups were compared pair-wise using ANOVA with a treatment effect after a logarithmic transformation on the tick or flea data (count +1) on each assessment day. In addition, the baseline counts were compared in the same way by an ANOVA across all groups.

RESULTS

Tick counts for the negative control group and the treated groups are shown in Table 1. Percent efficacy for the three treated groups is shown in Table 2.

Table 1. Mean Tick Counts in the Control Group and the Three Treatment Groups

DAY	GROUP 1 - Negative control		GROUP 2 – Test substance (104.05)		GROUP 3 - Test substance (104.05); Shampooed		GROUP 4 – Test substance (104.05); Water immersed	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]	Arithmetic mean	Geometric mean[2]	Arithmetic mean	Geometric mean[3]
-2	31.5	30.7[a]	29.8	29.5[a]	25.8	25.2[a]	29.7	29.4[a]
+2	27.2	25.7[a]	6.8	6.3[b]	10.5	9.1[b]	5.5	3.8[b]
+9	20.0	18.8[a]	0.0	0.0[b]	0.0	0.0[b]	0.0	0.0[b]
+16	25.3	22.9[a]	0.0	0.0[b]	0.0	0.0[b]	0.0	0.0[b]
+23	28.0	27.7[a]	0.0	0.0[b]	0.0	0.0[b]	0.0	0.0[b]
+30	30.8	30.6[a]	0.0	0.0[b]	0.2	0.1[b]	0.0	0.0[b]

[1] The groups did not differ statistically significantly (P>0.05) on Day -2
[2] Treatment Groups 2, 3 and 4 differed statistically significantly (P<0.05) from the negative control Group 1 on all post treatment assessment days
[3] Groups 4 differed statistically significantly (P<0.05) from Group 3 on Day 12

Table 2. Efficacy Values (%) Against Ticks for the Three Treatment Groups

DAY	EFFICACIES (%)					
	GROUP 2 – Test substance (104.05)		GROUP 3 - Test substance (104.05); Shampooed		GROUP 4 - Test substance (104.05); Water immersed	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean
+2	74.8	75.3	61.3	64.6	79.8	85.4
+9	100.0	100.0	100.0	100.0	100.0	100.0
+16	100.0	100.0	100.0	100.0	100.0	100.0
+23	100.0	100.0	100.0	100.0	100.0	100.0
+30	100.0	100.0	99.5	99.6	100.0	100.0

Flea counts for the negative control group and the treated groups are shown in Table 3. Percent efficacy for the three treated groups is shown in Table 4.

Table 3. Mean Flea Counts in the Control Group and the Three Treatment Groups

DAY	GROUP 1 - Negative control		GROUP 2 – Test substance (104.05)		GROUP 3 - Test substance (104.05); Shampooed		GROUP 4 – Test substance (104.05); Water Immersed	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[2]	Arithmetic mean	Geometric mean[2]	Arithmetic mean	Geometric mean[2]
-2	58.2	54.3[1]	48.8	47.7[1]	52.8	51.8[1]	45.3	43.3[1]
+2	51.3	47.9[1]	0.8	0.3[1]	3.7	1.4[1]	1.2	0.8[1]
+9	31.2	26.4[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+16	36.7	35.4[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+23	58.0	56.6[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+30	56.0	52.0[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]

[1] The groups did not differ statistically significantly (P>0.05) on Day -2

[2] Treatment Groups 2, 3 and 4 differed statistically significantly (P<0.05) from the negative control Group 1 on all post treatment assessment days

Table 4. Efficacy Values (%) Against Fleas for the Three Treatment Groups

DAY	EFFICACIES (%)					
	GROUP 2 – Test substance (104.05)		GROUP 3 - Test substance (104.05); Shampooed		GROUP 4 – Test substance (104.05); Water Immersed	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean
+2	98.4	99.0	92.9	97.0	97.7	98.4
+9	100.0	100.0	100.0	100.0	100.0	100.0
+16	100.0	100.0	100.0	100.0	100.0	100.0
+23	100.0	100.0	100.0	100.0	100.0	100.0
+30	100.0	100.0	100.0	100.0	100.0	100.0

Study Author's Conclusions

***Ticks*:** Efficacy values based on geometric means were considered primary. Therapeutic efficacies for Groups 2, 3, and 4 were 75.3%, 64.6% and 85.4%, respectively on Day +2. All treatment groups had >90% efficacy against ticks for the duration of the assessment period.

Fleas: Efficacy values based on geometric means were considered primary. Therapeutic efficacies for Groups 2, 3, and 4 were 99.0%, 97.0% and 98.4%, respectively, on Day +2. All treatment groups had 100% efficacy against fleas for all other assessment periods.

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when

tested under simulated or actual field conditions." Although the efficacy value for ticks on Day +2 were less than 90%, the recommended performance standard was reached in all three treatment groups by Day +9.

Reviewer's Recommendations

Acceptable, if the registrant can verify that the concentrations of the a.i. in the test product are the same as those in "Effitix Topical Solution for Dogs" or are within the certified upper and lower limits of the product as specified on the CSF. Results for ticks support the label claim that the product "kills ticks for at least a month". Results for fleas do not support the label claim "lasts for three months;" however, they can support a claim of efficacy for up to one month. Label does not have any claims concerning the efficacy against ticks or fleas after treated dogs are shampooed or are immersed in water.

Note: although not specifically stated in the study report, the reported test concentrations (6.7% fipronil and 50% permethrin) may be based on weight per volume measurements. Other MRIDs in Task 2-30 (e.g., MRID 48467I-26) indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-25. Moran, C. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%, Permethrin 50%) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Amblyoma americanum*) on Dogs. October 28, 2010

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
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Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-25**. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%, Permethrin 50%) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Amblyoma americanum)* on Dogs. Moran, C. October 28, 2010
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	I. Villard, Virbac SA
TESTING FACILITY:	Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland
STUDY DIRECTOR:	C. Moran, BSc, MAnSc
SUBMITTER:	I. Villard, Virbac SA
STUDY COMPLETED:	28/10/2010
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"The study was conducted in compliance with the OECD Principles of Good Laboratory Practice [ENV/MC/CHEM/(98)17]."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: Fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2

	mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.
PROPOSED LABEL MARKETING CLAIMS:	..can kill ticks for at least a month

STUDY REVIEW

Purpose: To determine the duration of efficacy of a single application of formulation 104.05 against infestations of ticks (*Amblyoma americanum*) on dogs.

MATERIALS AND METHODS

Test Location: Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland

Test Material(s): 104.05 spot-on formulation (nominal 6.7% w/v fipronil and 50% w/v permethrin). Two Certificates of Analysis was included in the study report (actual concentrations: 6.71 and 6.68% w/v fipronil and 50.26% and 50.23% w/v permethrin, respectively).

Test Species Name, Life Stage, Sex and Age: Male and female adult beagle and mixed breed dogs (*Canis familiaris*), ≥ 6 months old.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimatized for seven days. Dogs were grouped within one of two body weight bands; ≤17.9 kg or ≥18.0 kg based on Day -2 body weight measurements. Dogs ≥18.0 kg were ranked in decreasing order of Day -5 tick counts, irrespective of sex. The first two dogs ≥18.0 kg formed a block and were assigned to either the treatment group or the control group using random order numbers. The next two dogs ≥18.0 kg were blocked and assigned to groups in the same way, as was the third two dogs ≥18.0 kg. All remaining dogs were then ranked in decreasing order of Day -5 tick count, within each sex. The first two female dogs were assigned to one of the two groups using the same method as described above, followed by the second and third pair of females and then the remaining males until there were three males and three females in the treatment group and in the control group. Dogs were infested with approximately 50 ±4 viable, unfed adult *Amblyoma americanum* ticks (approximately 50% male and 50% female) on Days -7, 0, 7, 14, 21, 28, 35, and 42. On Day -5, about 48 hr post infestation, ticks were counted and removed from the dogs. On Day 1, ticks were counted, categorized by gender, attachment status, viability and location, but not removed. On Day 2, ticks were counted categorized and removed from the dogs approximately 48 hr after treatment. On Days 9, 16, 23, 30, 37 and 44, ticks were counted, categorized, and removed from the dogs approximately 48 hr post infestation.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One and one control group.

Number of individuals per replicate: Six.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 15-22°C; 53-80% RH

Data or endpoints collected/recorded: On Day 1, ticks were counted, categorized by gender, attachment status, viability and location, but not removed. On Day 2, ticks were counted categorized and removed from the dogs approximately 48 hr after treatment. On Days 9, 16, 23, 30, 37 and 44, ticks were counted, categorized, and removed from the dogs approximately 48 hr post infestation.

Data analysis: Primary efficacy was defined as the geometric mean live tick reduction when compared to the untreated control group. Efficacy was declared at ≥90% tick count reduction compared to the control group.

To calculate efficacy the number of live attached ticks was added to the number of live free ticks. This count was calculated after totaling male and female ticks over all locations from which ticks were collected.

Arithmetic and geometric mean tick counts were calculated for each assessment day and used to calculated percent reduction. The geometric mean was calculated by first applying a natural logarithmic transformation. In cases where the data sets included a zero, geometric means were calculated by adding 1 to all numbers before applying the transformations. The arithmetic mean was calculated for the transformed data. This was then antilogged and 1 was subtracted (if the data sets contained a zero).

Percent efficacy was calculated from Abbott's formula as follows:

Efficacy (% reduction) = 100 x [(Mc – Mt) / Mc], where:

Mc = Geometric mean count in the control group (Group 1) at a specific time point.
Mt = Geometric mean count in the treatment group (Group 2) at a specific time point.

The test and control groups were compared using ANOVA for Days 1, 2, 16, 23, 30, 37, and 44. For study Day 9 the comparisons were on the basis of the numbers of animals with tick present using the non-parametric Fisher's Exact test. All tests were two-tailed with a 5% level of significance.

RESULTS

Results for each individual test animal are included in the study report. Deviations from the study plan are listed below:

1. The Study Plan stated that for the duration of the study the dogs would be housed in Unit 2 at the Glenamoy facilities of Charles River Laboratories Preclinical Services Ireland Ltd. The animals were housed in Unit 1 at the Glenamoy facilities of Charles River Laboratories Preclinical Services Ireland Ltd. The deviation arose due to a mistake in the Study Plan, which was subsequently corrected by amendment. Since the pens used were of the correct size, as stated in Section 8.1 of the Study Plan, and the environmental conditions were the same in Unit 1 and Unit 2, there was no impact on the study.

2. Amendment 1 stated that only four female and five male dogs should weigh ≥18.0 kg on Study Day -7, and that six female and five male dogs should weigh ≤17.9 kg on Study Day -7. In fact four female and four male dogs weighing ≥18.0 kg on Study Day -7 and six female and six male dogs weighing ≤17.9 kg on Study Day -7 were included in the study. The deviation arose due to an oversight on the part of the Study Director. Since the correct number of animals of each weight band were assigned to groups on Study Day -1, there was no impact on the study.

3. The Study Plan stated that for the duration of the study the temperature should remain between 15°C and 21°C and the relative humidity between 30 % and 70 %. On 19AUG09 the temperature reached 22 °C and the relative humidity reached 73 %. On 20AUG09 the relative humidity reached up to 75 % in the morning, and 76% in the afternoon, on 21AUG09 the relative humidity reached 77 % in the morning, and on 25AUG09 the relative humidity reached 75 % in the morning. On 01SEP09 the relative humidity in the study unit reached 80%. Since there was no indication of discomfort or illness in the study animals, and ticks are comfortable in humid conditions there was no impact on the study.

4. As a consequence of the unforeseen occurrence (see Section 14.0 Unforeseen Occurrences above) which took place on 10SEP09 (Study Day 30) some tick count data for animals 15019, 28572, 59347 and 33610 on 03SEP09 (Study Day 23) was lost. As these data had been entered into Excel files and checked and the summary results of all tick counts for all animals are still available, the Study Director is satisfied that there is no impact on the study.

5. The Study Plan stated that during tick infestations all animals would remain in containment boxes for 1 hour (± 5 min) post infestation. On Study Day 7 (18AUG09) animal no. 33610 (Group 2, Test Item) was infested with ticks at 15:27 and removed from the tick containment box at 16:20 – a deviation of 2 minutes. The deviation occurred due to an oversight on the part of the technician who removed the animals from the tick containment boxes. Since the animal was kept in the tick containment box for 53 instead of 55 minutes, and as the attachment rates of ticks in the other animals assigned to Group 2 were similar to those for animal no. 33610, the Study Director is satisfied that this deviation would have had no impact on the study.

6. The Study Plan specified that the ticks would be stored between 85-100% RH at the Entomology Dept. at Charles River Laboratories Preclinical Services Ireland Ltd. While the ticks were stored in the Entomology Dept. at Charles River Laboratories Preclinical Services Ireland Ltd., the relative humidity range was 68% to 99%. As all ticks remained viable and as the attachment rate of the ticks was >25% on 6/8 infestation timepoints (mean % attachment rates were 22.3% and 24.4% on Study Days 1 and 9 respectively), the Study Director is satisfied that the low RH values during the storage period in the Entomology Dept. had no impact on the viability of the ticks or on the study.

7. Blinding was broken on one occasion (Study Day 16: 27AUG09) when the individual who checked the allocation to groups data, and who checked the target volume and dose times and witnessed administration of test item, also performed the tick count of animal no. 54047. As the tick count data from this animal were similar to those recorded for other animals assigned to Group 1 (untreated control) at this timepoint, and similar to the tick counts recorded at other timepoints for this animal, the Study Director is satisfied that the tick count performed on this animal was performed in an unbiased way, that the data are valid and that this deviation had no impact on the integrity of the study.

8. The Study Plan specified that the study would continue only if the efficacy of the test item remained above 80%. On Study Day 30, the efficacy of the test item was 79% but following consultation with the sponsor, it was agreed to continue the study. An amendment was not prepared by the Study Director to allow for the continuation of the study when the efficacy of the test item reached 79%. In the opinion of the Study Director, there was no impact of this deviation on the study as at a timepoint subsequent to Study Day 30 (i.e. Study Day 37, the efficacy of the test item increased to 88%.

Tick counts for the negative control group and the treated group are shown in Table 1.

Table 1. Tick Counts in the Control and Treated Groups

Group No. and Treatment	Animal No.	Study Day							
		1	2	9	16	23	30	37	44
1	64047	13	18	11	19	10	27	17	12
Control	69323	8	11	10	14	12	21	16	15
(No treatment)	87360	6	11	15	24	15	21	15	6
	11786	19	23	17	15	10	24	21	17
	49113	9	11	11	22	18	19	25	25
	24358	12	17	10	18	31	33	32	18
Total		67	91	74	112	102	145	126	93
2	01671I	14	5	0	1	1	7	5	9
104.05	23600	20	16	0	4	4	18	8	5
(0.1mL/kg bodyweight)	15019	17	2	0	2	4	13	12	17
	28572	4	3	0	0	0	4	1	2
	59347	9	7	2	0	3	3	0	7
	33510	9	2	0	0	0	0	0	0
Total		73	35	2	7	12	45	26	40

* Figures presented in this table include both Live Attached and Live Free Ticks.

The percent efficacy of the test product against *Amblyoma americanum* ticks, based on geometric and arithmetic means, for each assessment day was as follows:

- -3% (geometric means) and -9% (arithmetic means) on study day 1
- 70% (geometric means) and 62% (arithmetic means) on study day 2
- 98% (geometric means) and 97% (arithmetic means) on study day 9
- 96% (geometric means) and 94% (arithmetic means) on study day 16
- 91% (geometric means) and 88% (arithmetic means) on study day 23
- 79% (geometric means) and 69% (arithmetic means) on study day 30
- 88% (geometric means) and 79% (arithmetic means) on study day 37
- 69% (geometric means) and 57% (arithmetic means) on study day 44

Statistically significant differences between the control and treated group in number of live ticks were seen on Days 2, 16, 23, 30, 37, and 44.

Study Author's Conclusions

The results of this study demonstrate that a single administration of the Test Item (104.05: fipronil 6.7% w/v, permethrin 50% w/v) at a dose rate of 0.1 mL/kg bodyweight, to beagle and mixed breed dogs, was effective (efficacy ≥ 90%) against *A. americanum* on Study Days 9, 16 and 23 post treatment, with some residual control of ticks (efficacy was approximately 80%) on Study Day 30 and Study Day 37.

A single topical application of the Test Item (104.05) was well tolerated.

Reviewer's Conclusions

The results support the conclusions of the study author. Although adequate efficacy against *Amblyoma americanum* ticks was demonstrated on Days 9, 16 and 23, efficacy was only 79% on Day 30. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions."

Reviewer's Recommendations

Unacceptable. The label claim that the product kills ticks for at least a month, is not fully supported.

Note: The reported nominal test concentrations were 6.7% w/v fipronil and 50% w/v permethrin. Other MRIDs in Task 2-30 (e.g., MRID 484671-26) indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, respectively, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-26. Moran, C. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7% w/v, Permethrin 50% w/v) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Ixodes scapularis*) on Dogs. December 1, 2010

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
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Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-26.** The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7% w/v, Permethrin 50% w/v) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Ixodes scapularis*) on Dogs. Moran, C. December 1, 2010.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	I. Villard, Virbac SA
TESTING FACILITY:	Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland
STUDY DIRECTOR:	C. Moran, BSc, MAnSc.
SUBMITTER:	I. Villard, Virbac SA
STUDY COMPLETED:	22/03/2010
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"The study was conducted in compliance with the OECD Principles of Good Laboratory Practice [ENV/MC/CHEM/(98)17]."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not

provided.

PROPOSED LABEL MARKETING CLAIMS: ..can kill ticks for at least a month.

STUDY REVIEW

Purpose: To determine the duration of efficacy of a single application of formulation 104.05 against infestations of ticks (*Ixodes scapularis*) on dogs.

MATERIALS AND METHODS

Test Location: Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland

Test Material(s): 104.05 spot-on formulation (Nominal 6.7% w/v fipronil and 50% w/v permethrin w/v; equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin). Actual concentrations of two analyses: 6.75% w/v fipronil w/v and 51.36% w/v permethrin, and 6.68% w/v fipronil w/v and 50.23% w/v permethrin. Certificates of Analysis included in study report.

Test Species Name, Life Stage, Sex and Age: Male and female adult beagle and mixed breed dogs (*Canis familiaris*), ≥ 6 months old.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Animals were housed singly in rooms measuring approximately 2 m x 2 m x 2 m and acclimatized for seven days prior to testing. Animals were grouped within one of two body weight bands; ≤17.9 kg or ≥18.0 kg based on Day -2 body weight measurements. Dogs ≥18.0 kg were ranked in decreasing order of Day -5 tick counts, irrespective of sex. The first two dogs ≥18.0 kg formed a block and were assigned to either the treatment group or the control group, using random order numbers. The next two dogs ≥18.0 kg were blocked and assigned to groups in the same way, as was the third two dogs ≥18.0 kg. All remaining dogs were then ranked in decreasing order of Day -5 tick count, within each sex. The first two female dogs were assigned to one of the two groups using the same method as described above, followed by the second and third pair of females and then the remaining males until there were three male and three females in the treatment group and in the control group. Dogs were infested with approximately 40 ±4 viable, unfed adult ticks *Ixodes scapularis* (25 ± 2 females and 15 ± 2 males) on Day -7, and with 50 ±4 ticks (30 ± 2 females and 20 ± 2 males) on Days 0, 7, 14, 21, 28, 35, and 42, and with 35 ±4 (30 ± 2 females and 5 ± 1 males) on Day 49. On Day 0, the dogs were infested with ticks 2 hr ± 10 min prior to being treated. Dogs were sedated to facilitate tick infestation and tick counting. Group #2 dogs were treated once on Day 0 (2 hr ± 4 min post infestation). Group #1 dogs were not treated. Ticks were counted, categorized and removed from the dogs on Days -5, 2, 9, 16, 23, 30, 37, 44, and 51, approximately 48 hr post infestation. Ticks were counted and categorized but not removed from the dogs on Day 1. The number, sex, attachment status, viability and location on the dog of each tick were recorded at each assessment time.

Treatments, including untreated control: Maximum of 0.1 mL/kg.

Number of replicates per treatment: One.

Number of individuals per replicate: Three males and three females in the treated group and the same numbe rof each in the control group.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 15-20°C; 25-65% relative humidity.

Data or endpoints collected/recorded: The number, sex, attachment status, viability and location on the dog of each tick were recorded at each assessment time.

Data analysis: Efficacy calculations were based on geometric means, and specifically on the geometric means of the live free and attached female tick counts. The geometric mean was calculated by first applying a natural logarithmic transformation. In cases where the data set contained a zero, a "1" was added to all numbers before applying the transformation. The arithmetic mean was calculated for the transformed data. This was then anti-logged and "1" was subtracted (if the data sets contained a zero).

Efficacy was calculated using Abbott's formula as follows:

Percent reduction (Efficacy = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric or arithmetic mean count in the control group (Group 1) at a specific time point.
Gm_t = Geometric or arithmetic mean count in the treatment group (Group 2) at a specific time point.
The test and control groups were compared using ANOVA for Study Days 1, 2, 30, 37, 44, and 51. For Study days 9, 16, and 23, comparisons were on the basis of the numbers of animals with ticks present using the non-parametric Fisher's exact Test.

RESULTS

Data for each individual test animal and control are included in the study report. Data were adjusted for control mortality using Abbott's formula. Deviations from the study plan included:

1. On Study Day 37 sedation was reversed in two dogs before the 90 min time period specified in the protocol
2. The minimum relative humidity in the tick storage cabinet on most days was less than the 85% specified in the protocol, but with the exception of 9 data points it was >75% (within 10% of the acceptable range).
3. The maximum relative humidity was below the specified range on two occasions when it was 36 and 84%.

Tick counts for the control group and the treated group for each time interval are shown in Table 1. Percent efficacy for each time interval is shown in Table 2.

Table 1. Total Live Female Tick Counts

Group No. and Treatment	Animal No.	Study Day 1	2	9	16	23	30	37	44	51
1	62807	17	19	27	17	22	18	23	21	15
Control	29561	17	21	25	14	20	22	22	7	16
(No treatment)	70872	13	19	20	10	16	12	21	19	21
	44062	23	23	28	12	23	25	20	23	26
	21577	15	16	23	19	22	24	22	19	18
	24343	12	19	26	16	23	14	23	16	24
Total		97	116	149	87	134	115	131	99	119
2	99561	5	0	0	0	0	1	1	5	5
104.05	57019	2	0	0	0	0	2	0	6	5
(0.1mL/kg cody weight)	71860	10	1	0	0	0	0	0	0	4
	29532	0	2	0	0	0	0	0	0	0
	73621	6	2	0	0	1	3	4	5	5
	32709	6	5	0	0	0	0	1	4	1
Total		43	10	0	0	1	6	15	22	24

[1] Figures presented in this table include both Live Attached Female and Live Free Female Ticks.
Each animal was infested with 30±2 female *Ixodes scapularis* on Study Days 0, 7, 14, 21, 28, 35, 42 and 49.

Table 2. Percent Efficacy Based on Arithmetic and Geometric Means of 104.05 Against *Ixodes scapularis* Ticks.

Day	Arithmetic Mean (%)	Geometric Mean (%)
1	56	59
2	91	94
9	100	100
16	100	100
23	99	99
30	95	96
37	89	93
44	76	83
51	80	85

Study Author's Conclusions

Analysis of homogenity indicated that there were no differences between the control and test groups in terms of body weight or tick counts on Study Day -5.

The test product was effective (≥90% efficacy) against *Ixodes scapularis* ticks on Study Days 2, 9, 16, 23, 30, and 37, with some residual control on Days 44 (83%) and 51 (85%).

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was reached for over one month.

Reviewer's Recommendations

Acceptable. Results support the label claim that the test product, formulation 104.05, kills ticks for at least one month, although 100% mortality was only achieved at two time intervals.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-27. Monzali, C. 2011. Determination of of a Combination of Fipronil and Permethrin in Topical Solution Against Mosquitoes (*Aedes aegypti*) on Dogs.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
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Angela M. Edmonds, B.S.

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Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	484671-27. Determination of of a Combination of Fipronil and Permethrin in Topical Solution Against Mosquitoes (*Aedes aegypti*) on Dogs. Monzali, C. April 6, 2011.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau, Virbac SA
TESTING FACILITY:	Avogadro, Parc de Génibrat, 31470 Fontenilles, France
STUDY DIRECTOR:	C. Monzali.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	06/04/2011
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study... was performed in accordance with....and the principles of Good Laboratory Practices including: EC principles of Good Laboratory Practices (Directive 2004/10/EC of the European Parliament and Council of the 11 FEB 2004)..."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: Fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not

provided.

PROPOSED LABEL MARKETING CLAIMS:	"... (prevents blood feeding by) (and) (kills) (and) (repels) ... mosquitoes for up to 4 weeks (a[one] month). Kills mosquitoes for up to four weeks (a[one] month)."

STUDY REVIEW

Purpose: To test the efficacy of 104.05 topical solution against *Aedes aegypti* mosquitoes on dogs.

MATERIALS AND METHODS

Test Location: Avogadro, Parc de Génibrat, 31470 Fontenilles, France

Test Material(s): 104.05 topical solution (6.7% w/v fipronil and 50% w/v permethrin). A Certificate of Analysis for the test product was included in the study report.

Test Species Name, Life Stage, Sex and Age: Short hair Beagle dogs and long hair Golden retriever cross dogs (10 males, 5 short hair and 5 long hair) and 4 females (short hair); age 8.8-15.3 months; weights 9.0-11.3 kg for the beagles and 20.8-27.4 kg for the retrievers.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 12 days prior to treatment during which time they were tested for ability to host mosquitoes by being exposed for 30 min to 40-67 unfed female mosquitoes (*A. aegypti*) at least 2 days old. Dogs allowing a feeding rate of >40% were considered good hosts. Twelve animals were randomly allocated into two groups: one control group of six animals (2 long hair males, 2 short hair males and 2 short hair females); and one test group of treated animals (2 long hair males; 2 short hair males and 2 short hair females). Six blocks of animals were formed based on body weight, and one animal from each block was randomly assigned to one of the two groups. Two animals were swapped in order to balance the groups with respect to the results of the infestation received during acclimatization. The test product (0.1 mL/kg) was administered to the dogs in the treatment group (between the shoulder blades) on Day 0. After treatment the dogs were kept in individual pens. The dogs in both groups were exposed for 28-35 min to unfed female mosquitoes on Day 1 (91-114 mosquitoes), Day 7 (88-108), Day 14 (51-121), Day 21/22 (44-110), Day 28 (87-111) and Day 35-37 (89-136). Dogs were sedated during infestations. Afterwards, the mosquitoes were collected, the dogs removed from the exposure cages and returned to their housing, and at 52-92 min after the beginning of the exposure, dead and alive mosquitoes were counted. The mosquitoes were frozen, crushed to determine if they had a blood meal and then the number of fed and unfed mosquitoes was determined.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One.

Number of individuals per replicate: Six in the treated group and six in the control group.

Length of exposure to treatment (time in seconds, minutes or hours): Topical application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 14.4-21.0°C; 16-80% RH; 12/12 light cycle.

Data or endpoints collected/recorded: Mosquito mortality rate (%) as well as mosquito blood feeding rate (%) were determined.

Data analysis: Efficacy calculations were calculated from Abbott's formula, by comparing the geometric mean number of blood fed mosquitoes from the treated group to the geometric mean of the number of blood fed mosquitoes from the control group:

Anti-feeding Efficacy (%) = 100 x [(FC – FT)/FC], where:

FC = geometric mean of the number of blood fed mosquitoes from the control group
FT = geometric mean number of blood fed mosquitoes from the treated group

The killing efficacy was determined by comparing the mortality of mosquitoes between the control and treated groups after the 30-min exposure period:

Killing Efficacy (%) = 100 x [(LC – LT)/LC], where:

LC = geometric mean number of live mosquitoes in the control group.
FT = geometric mean number of live mosquitoes in the treated group.

RESULTS

Individual animal results were presented in the study report. Deviations from the study protocol were as listed below:

- The two animals nos.160612 and 251448 were housed in the treated group room since 09 FEB 2010 but were treated 8 days later, on 17 FEB 2010.

- During acclimatisation: dogs were exposed to 40 – 67 unfed female mosquitoes (*A. aegypti*) of at least 2 days old instead of 50 ± 5. During the other infestations, dogs were exposed to 87 – 136 unfed female mosquitoes instead of 100 ± 10 and 44 – 63 unfed female mosquitoes instead of 50 ± 5 at Day 14, for the 4 dogs nos.251092, 251448, 258217 and 160612 and Day 21 for the 8 dogs nos.251561, 258329, 251819, 258075, X1PAL2, X2PAC9, X1PAC6 and X2PAD2.

- Dog no.258329, from Day 10 to Day 37, received 600g of food daily in two times instead of 300g once daily, because he lost weight. Times of the second food distribution were not recorded in the raw data.

- Dogs were fed between 3 hours 07 minutes and 7 hours 52 minutes instead of about four hours post exposure.

- Some dogs received an anti-parasitic treatment within two months before Day 0: short hair dog no.251092 received an anthelminthic treatment (fenbendazole) on 24 DEC 2009 and the five long hair dogs nos.2GHP252, X1PAL2, X2PAC9, X1PAC6 and X2PAD2 received an ear anti-parasitic treatment (fipronil 10%, approximately 1mg/kg) on 18 JAN 2010. These treatments had no repellent or killing impact on mosquitoes.

- Maximum and minimum temperatures and relative humidity of treated dogs room were not recorded on the last day of the in-life phase (27 MAR 2010).

- The 4 dogs nos.251092, 251448, 258217 and 160612 were infested at Day 22 instead of Day 21 and Day 37 instead of Day 35 because of an insufficient number of unfed female mosquitoes of at least 2 days old. Nevertheless, we can consider that Day 22 was equivalent to Day 21 and Day 37 was equivalent to Day 35.

- For dog no.251819, the test item dose volume was rounded to the nearest 0.05 mL, instead of the nearest 0.1 mL.

- Temperature in the exposition room was maintained between 23.2°C and 31.2°C, instead of 24°C and 30°C, and relative humidity was maintained between 40 and 95%, instead of 40 and 80%.

- Dogs were exposed to female mosquitoes for 28 to 35 minutes instead of 30 minutes and dead and alive mosquitoes were counted at 52 minutes to 1h32 (corresponding to 92 minutes) post beginning of exposure, instead of 60 minutes.

Mosquito mortality rates are shown in Table 1. Mosquito blood feeding rates are shown in Table 2. Mosquito anti-feeding efficacy and mosquito killing efficacy of Product 104.05 are shown in Table 3.

Table 1. Mosquito Mortality Rates (%) in Control and Treated Dogs

Long + short hair dogs		Time						
Group	Mosquito mortality rate (%)	Acclimati-sation	Day 1	Day 7	Day 14	Day 21/22	Day 28	Day 35/37
untreated	arithmetic mean	0.0	0.2	0.2	0.0	0.0	0.0	0.0
	SD	0.0	0.4	0.4	0.0	0.0	0.0	0.0
	geometric mean	0.0	0.1	0.1	0.0	0.0	0.0	0.0
treated	arithmetic mean	0.0	33.5	36.2	34.8	27.9	31.2	22.2
	SD	0.0	25.7	28.1	28.1	21.4	20.8	24.8
	geometric mean	0.0	24.6	19.1	19.4	13.5	22.9	13.0

Table 2. Mosquito Blood Feeding Rates in Control and Treated Groups

Long + short hair dogs		Time						
Group	Mosquito blood feeding rate (%)	Acclimati-sation	Day 1	Day 7	Day 14	Day 21/22	Day 28	Day 35/37
untreated	arithmetic mean	75.9	51.7	68.8	71.4	53.3	72.1	41.0
	SD	23.5	25.4	13.4	17.8	22.8	20.3	24.1
	geometric mean	72.1	43.4	67.6	69.6	49.5	69.4	34.2
treated	arithmetic mean	68.9	10.6	9.1	18.8	11.1	24.1	28.2
	SD	26.5	5.4	8.6	14.4	5.0	9.0	14.8
	geometric mean	63.4	9.3	6.2	13.5	9.7	22.6	25.3

Table 3. Mosquito Anti-Feeding Efficacy and Mosquito Killing Efficacy of Product 104.05

	Efficacy (%)	Day 1	Day 7	Day 14	Day 21/22	Day 28	Day 35/37
Anti-feeding efficacy	Short hair	87.4	96.2	86.1	77.6	77.9	52.5
	Long hair	43.1	65.2	55.9	84.5	39.6	-156.7
	Global	79.2	91.7	79.3	79.8	69.1	17.1
Killing efficacy	Short hair	50.6	59.5	53.9	43.4	43.6	26.0
	Long hair	11.5	6.9	-8.0	-5.5	21.8	-2.5
	Global	40.0	46.5	38.6	30.4	37.1	17.5

Study Author's Conclusions

Short-haired dogs were more susceptible to mosquitoes than long hair dogs. The test product had a more effective anti-feeding (repellency) action than a killing action, especially in short hair dogs. Killing efficacy was no greater than 59.5% (Day 7 for short hair dogs). Anti-feeding efficacy for short and long hair dogs combined was only greater the 90% for one time interval (Day 7).

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard for killing efficacy was not reached in this study. Anti-feeding efficacy (repellency) reached 90% at only one time interval, Day 7.

Reviewer's Recommendations

Unacceptable. The study results do not support the label claim that the product "...(prevents blood feeding by) (and) (kills) (and) (repels) ... mosquitoes for up to 4 weeks (a [one] month). Kills mosquitoes for up to four weeks (a[one] month)."

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-28. Fourie, J.J. Repellence Efficacy Study of 104.05 Against Ticks (*Dermacentor variabilis* and *Rhipicephalus sanguineus*) on Dogs Under Laboratory Conditions. November 3, 2010.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
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Date: OCT 19 2011

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Robert Ross, M.S., Program Manager

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Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: Jennifer Goldberg
Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-28.** Repllence Efficacy Study of 104.05 Against Ticks (*Dermacentor variabilis* and *Rhipicephalus sanguineus*) on Dogs Under Laboratory Conditions. Fourie, J.J. November 3, 2010.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau, MD, Virbac SA
TESTING FACILITY:	ClinVet International, Uitzich Road, Bainsvlei, Bloemfontein, Republic of South Africa
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	21/07/2010
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: Fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided

FORMULATION TYPE: Topical solution

PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb
ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.

PROPOSED LABEL MARKETING CLAIMS: ..can kill ticks for at least a month.

STUDY REVIEW

Purpose: To test the repellence efficacy, tick killing effect, and tick viability impact of 104.05 spot-on formulation against *Dermacentor variabilis* and *Rhipicephalus sanguineus* ticks on dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitzich Road, Bainsvlei, Bloemfontein, Republic of South Africa

Test Material(s): 104.05 spot-on formulation (6.7% w/v fipronil and 50% w/v permethrin, equivalent to 6.01% w/w firpronil and 44.88% w/w permethrin).

Test Species Name, Life Stage, Sex and Age: Male and female sub adult and adult dogs (*Canis familiaris*) greater than 6 months old; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment (Day -7 to Day -1); dewormed and "did not harbor ticks." Dogs were kept in individual pens 1.9 m by 2.97 m. Twelve dogs were used in the study; 8 dogs <18.14 kg and 4 dogs ≥18.14 kg. The 8 dogs of the smaller weight were blocked into four blocks of two dogs each, and the large dogs were blocked into two blocks of two dogs each. Within each block the dogs were randomly assigned to either Group #1 (negative control) or Group #2 (treated group). Dogs were dosed with 0.1 mL of the test product on Day 0.

Laboratory breed strains of *Dermacentor variabilis* and *Rhipicephalus sanguineus* ticks were used in the artificial infestations. Immature ticks were fed on rabbits. The dogs were infested with 30 unfed adult ticks in an infestation chamber on Day -6 (*R. sanguineus* only), and Days +1, +3, +7, +14, +21, +22, and +28. In situ tick assessments were conducted on Days +1, +3, +7, +14, +21, +22, and +28, 3 hours after infestation. Tick counts, and removals were conducted on Day -5, +2, +4, +8, +15, +22, +23, and +29, 24 hours after the infestations.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One treated group and one control group.

Number of individuals per replicate: Six treated and six controls.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: ~20±4°C; 12/12 light cycle.

Data or endpoints collected/recorded: In situ tick assessments were conducted on Days +1, +3, +7, +14, +21, +22, and +28, 3 hours after infestation; tcks were counted but not removed. Ticks were counted and removed on Day -5, +2, +4, +8, +15, +22, +23, and +29, 24 hours after the infestations. The ticks were categorized as being alive or killed and also in three subgroups: free, or attached and unengorged, or attached and engorged (the latter category was not included during the in situ observations). The ticks counted and removed during the 24 hr assessments were categorized according to sex. Ticks found in the infestation chamber after removal of the dogs were categorized as alive, moribund or dead. Dogs were sedated to facilitate tick infestation.

Data analysis: Efficacy calculations were made for each treatment group at each assessment interval. Efficacy was based on geometric means of the tick data (count +1) because of the anticipated low and possibly zero counts at some time period and the likelihood that a normal distribution would not be seen. One was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group.

In situ tick count efficacy was calculated as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live ticks (alive, free and attached) on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live ticks (alive, free and attached) on dogs in the treatment group (Group 2) at a specific time point.

The groups were compared using an ANOVA with a treatment effect after a logarithmic transformation on the tick data (count +1)

24 hour tick count and removal efficacies were calculated for each species of tick as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live ticks (alive, free and attached, unengorged and engorged) on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live ticks (alive, free and attached, unengorged and engorged) on dogs in the treatment group (Group 2) at a specific time point.

The groups were compared using an ANOVA with a treatment effect after a logarithmic transformation on the tick data (count +1)

RESULTS

Data sheets with the individual animal results were included in the study report. Amendments to and deviations from the test protocol are shown below:

Protocol amendment	
Amendment #1:	Effective date 13 July 2010, to the effect that the Day +21 tick (*Dermacentor variabilis* and *Rhipicephalus sanguineus*) infestations and subsequent assessments were repeated on Day +22.
Reason for change:	The attachment of *Dermacentor variabilis* ticks to the dogs were less than expected resulting in low tick counts on the study groups. The low number of ticks which attached could be due to a decrease in tick viability and it was decided to repeat the infestations with a different batch of *Dermacentor variabilis* ticks.
Impact on study:	No foreseen negative impact. Additional results for the week 3 assessments were obtained from the repeated infestation and subsequent assessments.
Protocol deviation	
Deviation #1:	Effective date 20 Aug 2010 to the effect that temperatures in Unit 19 Section E deviated from 01 Jul to 04 Jul 2010 between 0.6 – 1.6 °C from the ranges specified in the protocol.
Reason for deviation:	Air conditioning unit malfunction
Impact on study:	No negative impact
Deviation #2:	Effective date 22 June to 21 July that the maximum temperatures recorded in the temperature controlled room with the humidity containers containing the ticks for viability assessments exceeded the protocol specified maximum temperature of 28°C with up to 1°C on a number of occasions.
Reason for deviation:	Air conditioning unit malfunction
Impact on study:	No negative impact

***Results for Rhipicephalus sanguineus*:**

Twenty-four hour tick counts are shown in Table 1. Twenty-four hour killing efficacy values are shown in Table 2. Three-hour in situ tick counts are shown in Table 3, and 3-hr efficacy values in Table 4. Repellency data for 10-min exposures are shown in Table 5 and tick viability after the 10 min exposures is shown in Table 6.

Table 1. 24-hr Counts of *Rhipicephalus sanguineus* in Control and Treated Groups

DAY	GROUP 1 - Negative control		GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]
+2	13.2	11.8	0.2	0.1
+4	13.3	12.1	0.0	0.0
+8	12.8	11.3	0.0	0.0
+15	15.2	14.1	0.0	0.0
+22	14.7	13.4	0.0	0.0
+23	18.8	18.2	0.0	0.0
+29	14.2	14.0	0.0	0.0

[1]*Group 2 differed statistically significantly (p<0.05) from the negative control Group 1 on all days.*

Table 2. 24-hr Efficacy of Product 104.05 Against *Rhipicephalus sanguineus*

DAY	EFFICACIES (%)	
	GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean
+2	98.7	99.0
+4	100.0	100.0
+8	100.0	100.0
+15	100.0	100.0
+22	100.0	100.0
+23	100.0	100.0
+29	100.0	100.0

Table 3. 3-hr Counts of *Rhipicephalus sanguineus* in Control and Treated Groups

DAY	GROUP 1 - Negative control		GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]
+1	13.2	12.1	3.7	2.8
+3	14.7	14.1	3.2	1.4
+7	14.5	13.7	0.8	0.6
+14	16.2	15.7	1.0	0.6
+21	16.8	15.8	3.0	1.9
+22	17.0	16.6	2.2	1.7
+28	17.3	17.2	3.8	3.7

[1]*Group 2 differed statistically significantly (p<0.05) from the negative control Group 1 on all days.*

Table 4. 3-hr Efficacy of Produet 104.05 Against *Rhipicephalus sanguineus*

DAY	EFFICACIES (%)	
	GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean
+1	72.2	77.1
+3	78.4	90.3
+7	94.3	95.7
+14	93.8	95.9
+21	82.2	88.2
+22	87.3	90.0
+28	77.9	78.4

Table 5. Repellency Effect of Formulation 104.05 Against *Rhipicephalus sanguineus*

Day	Treatment Group	Mean number of ticks[1]	% Repelled[2]	% Difference vs. Control[3]
+1	Group 1 - Negative control	0.1	0.1	3.1
	Group 2 – IVP (104.05)	1.1	3.2	
+3	Group 1 - Negative control	0.3	0.4	2.5
	Group 2 – IVP (104.05)	1.0	2.9	
+7	Group 1 - Negative control	0.4	0.8	16.7
	Group 2 – IVP (104.05)	5.2	17.5[4]	
+14	Group 1 - Negative control	0.0	0.0	5.4
	Group 2 – IVP (104.05)	1.7	5.4[4]	
+21	Group 1 - Negative control	0.3	0.5	1.1
	Group 2 – IVP (104.05)	0.7	1.6	
+22	Group 1 - Negative control	0.0	0.0	3.3
	Group 2 – IVP (104.05)	1.1	3.3[4]	
+28	Group 1 - Negative control	0.2	0.2	6.4
	Group 2 – IVP (104.05)	1.9	6.6[4]	

[1] *Geometric mean number of total ticks (dead or alive) recovered from the infestation chamber.*
[2] *Average percent repelled, based on the number of ticks (30) initially infested.*
[3] *Percentage repelled: Difference (Group 2 – Group 1).*
[4] *Group 2 differed statistically significantly ($p<0.05$) from Group 1.*

Table 6. Viability of *Rhipicephalus sanguineus* After 10-min Exposures to Formulation 104.05

Day	Treatment Group	Mean number of ticks[1]	% Ticks dead or moribund[2]			
			10 min	3 Hr	24 Hr	48 Hr
+1	Group 1 - Negative control	0.1	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.1	6.7	17.9	75.0[3]	75.0[3]
+3	Group 1 - Negative control	0.3	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.0	0.0	1.7	60.2[3]	60.2[3]
+7	Group 1 - Negative control	0.4	0.0	0.0	0.4	1.2
	Group 2 – IVP (104.05)	5.2	0.0	62.0[3]	96.6[3]	97.8[3]
+14	Group 1 - Negative control	0.0	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.7	0.0	38.6[3]	65.7[3]	65.7[3]
+21	Group 1 - Negative control	0.3	0.0	0.0	0.0	6.7
	Group 2 – IVP (104.05)	0.7	0.0	8.2	37.1	37.1
+22	Group 1 - Negative control	0.0	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.1	0.0	2.5	6.7	6.7
+28	Group 1 - Negative control	0.2	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.9	0.0	0.0	0.0	32.8

[1] *Geometric mean number of total ticks (dead or alive) recovered from the infestation chamber*
[2] *Cumulative percent of ticks dead or moribund following exposure to treated dogs.*
[3] *Group 2 differed statistically significantly ($p<0.05$) from Group 1.*

Results for Dermacentor variabilis

Twenty-four hour tick counts are shown in Table 7. Twenty-four hour killing efficacy values are shown in Table 8. Three-hour in situ tick counts are shown in Table 9, and 3-hr efficacy values in Table 10. Repellency data for 10-min exposures are shown in Table 11, and tick viability after the 10-min exposures is shown in Table 12.

Table 7. 24-hr Counts of *Dermacentor variabilis* in Control and Treated Groups

DAY	GROUP 1 - Negative control		GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]
+2	19.8	18.4	0.7	0.4
+4	19.0	17.4	0.0	0.0
+8	14.7	14.0	0.0	0.0
+15	3.2	2.5	0.0	0.0
+22	5.0	4.2	0.0	0.0
+23	3.0	2.7	0.0	0.0
+29	12.3	11.2	0.3	0.3

[1]*Group 2 differed statistically significantly (p<0.05) from the negative control Group on all days.*

Table 8. 24-hr Efficacy of Product 104.05 Against *Dermacentor variabilis*

DAY	EFFICACIES (%)	
	GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean
+2	96.6	97.6
+4	100.0	100.0
+8	100.0	100.0
+15	100.0	100.0
+22	100.0	100.0
+23	100.0	100.0
+29	97.3	97.7

Table 7. 3-hr Counts of *Dermacentor variabilis* in Control and Treated Groups

DAY	EFFICACIES (%)	
	GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean
+1	69.6	78.2
+3	87.3	91.6
+7	91.4	94.3
+14	86.5	91.5
+21	91.2	95.2
+22	94.6	96.6
+28	79.1	80.2

Table 8. 3-hr Efficacy of Product 104.05 Against *Dermacentor variabilis*

DAY	GROUP 1 - Negative control		GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]
+1	24.7	24.3	7.5	5.3
+3	22.3	22.0	2.8	1.8
+7	17.5	17.1	1.5	1.0
+14	8.7	8.2	1.2	0.7
+21	5.7	5.4	0.5	0.3
+22	6.2	6.0	0.3	0.2
+28	18.3	17.8	3.8	3.5

[1]*Group 2 differed statistically significantly (p<0.05) from the negative control Group 1 on all days.*

Table 9. Repellency Effect of Formulation 104.05 Against *Dermacentor variabilis*

Day	Treatment Group	Mean number of ticks[1]	% Repelled[2]	% Difference vs. Control[3]
+1	Group 1 - Negative control	0.1	0.1	29.1
	Group 2 – IVP (104.05)	7.5	29.2[4]	
+3	Group 1 - Negative control	1.1	3.1	35.8
	Group 2 – IVP (104.05)	10.1	38.9[4]	
+7	Group 1 - Negative control	3.2	11.5	47.4
	Group 2 – IVP (104.05)	16.9	58.9[4]	
+14	Group 1 - Negative control	9.6	40.5	34.6
	GROUP 2 – IVP (104.05)	21.2	75.1	
+21	Group 1 - Negative control	10.2	43.1	26.6
	Group 2 – IVP (104.05)	20.4	69.7	
+22	Group 1 - Negative control	12.8	46.0	29.3
	GROUP 2 – IVP (104.05)	22.0	75.3[4]	
+28	Group 1 - Negative control	2.8	9.8	48.0
	Group 2 – IVP (104.05)	16.0	57.8[4]	

[1] *Geometric mean number of total ticks (dead or alive) recovered from the infestation chamber.*
[2] *Average percent repelled, based on the number of ticks (30) initially infested.*
[3] *Percentage repelled: Difference (Group 2 – Group 1).*
[4] *Group 2 differed statistically significantly ($p<0.05$) from Group 1.*

Table 10. Viability of *Dermacentor variabilis* After 10-min Exposures to Formulation 104.05

Day	Treatment Group	Mean number of ticks[1]	% Ticks dead or moribund[2]			
			10 min	3 Hr	24 Hr	48 Hr
+1	Group 1 - Negative control	0.1	0.0	0.0	6.7	6.7
	Group 2 – IVP (104.05)	7.5	0.2	52.7[3]	82.6[3]	94.5[3]
+3	Group 1 - Negative control	1.1	0.0	0.0	0.8	0.8
	Group 2 – IVP (104.05)	10.1	0.0	28.4[3]	55.7[3]	58.3[3]
+7	Group 1 - Negative control	3.2	0.0	0.0	0.0	1.7
	Group 2 – IVP (104.05)	16.9	0.0	6.7[3]	45.9[3]	66.7[3]
+14	Group 1 - Negative control	2.21	0.0	0.0	2.1	3.6
	Group 2 – IVP (104.05)	21.2	0.0	0.7	18.2[3]	25.8[3]
+21	Group 1 - Negative control	10.2	0.0	0.0	4.3	12.8
	Group 2 – IVP (104.05)	20.4	0.0	0.1	16.3	33.9
+22	Group 1 - Negative control	12.8	0.0	0.0	0.0	4.6
	Group 2 – IVP (104.05)	22.0	0.0	0.6	2.4[3]	23.3
+28	Group 1 - Negative control	2.8	0.0	0.0	0.0	2.8
	Group 2 – IVP (104.05)	16.0	0.0	0.0	0.0	15.8

[1] *Geometric mean number of total ticks (dead or alive) recovered from the infestation chamber.*
[2] *Cumulative percent of ticks dead or moribund following exposure to treated dogs.*
[3] *Group 2 differed statistically significantly ($p<0.05$) from Group 1.*

Study Author's Conclusions

Results of this study indicate that dogs treated with Formulation 104.05 at a dosage of 0.1 mL/kg were protected from infestations of *Dermacentor variabilis* and *Rhipicephalus sanguineus* for up to 29 days post treatment. Efficacy against *Rhipicephalus sanguineus* was 99% at Day +2 and 100% on all other assessment days. Efficacy against *Dermacentor variabilis* was 97.6% on Day +2 and 100% on every other assessment day except Day +29 when it was 97.7%.

Tick counts conducted 3-hr post treatment indicated that the test product was effective against both species throughout the study. Three-hour efficacy values ranged from 77.1 to 95.9% for *Rhipicephalus sanguineus* and from 78.2 to 96.6% for *Dermacentor variabilis*.

The repellent effect of formulation 104.05 after 10-min exposures was ≤ 16.7% for *Rhipicephalus sanguineus* and 26.6 to 48.0% for *Dermacentor variabilis*.

Unattached *Rhipicephalus sanguineus* tick viability values after the 10-min exposures were very variable due to the small numbers of ticks repelled (mean values of 0.7 to 5.2 were recorded for the treated group); however, a marked difference in the percentage of ticks found dead and moribund was observed between the ticks exposed to the test product and the controls (statistically significant by 3 hr on Days +7 and +14, and by 24 hr on Day +3 and +7). For *Dermacentor variabilis* similar results were obtained, with statistically significant differences from controls seen by 3 hr on Day +1, +3, and +7 and by 24 hour on Day +14.

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was reached for both species of tick for all assessment periods. The concentrations of the active ingredients in the test product were not verified or supported by a Certificate of Analysis.

Reviewer's Recommendations

Acceptable. However, the concentrations of the active ingredients in the test product were not verified by the registrant. Results support the label claim that the test product kills ticks for at least a month.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-29. Villard, I. Summary of Efficacy Data for Effitix™ Topical Solution for Dogs (Fipronil 6.01% and Permethrin 44.88% End Use Product). April 20, 2011.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX™ TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

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Date: OCT 19 2011

Robert Ross, M.S., Program Manager

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Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: _____
Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-29.** Summary of Efficacy Data for Effitix™ Topical Solution for Dogs (Fipronil 6.01% and Permethrin 44.88% End Use Product). Villard, I. April 20, 2011.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	C. Parks, Virbac SA
TESTING FACILITY:	N/A
STUDY DIRECTOR:	N/A
SUBMITTER:	C. Parks, Virbac SA
STUDY COMPLETED:	20/04/2011
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This document is a compilation document and is not subject to the requirements of 40 CFR Part 160."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not

provided.

PROPOSED LABEL MARKETING CLAIMS:	**Fleas:** ...can start killing adult fleas within 6 hr and lasts for up to three months... **Ticks:** ..can kill ticks for at least a month... **Lice:** can kill sucking biting and chewing lice for a month or longer... **Mites:** ...kills mites... **Biting flies and mosquitoes:** ...(prevents blood feeding by)(and)(kills)(and)(repels) biting flies and mosquitoes for up to 4 weeks (a[one] month). Kills mosquitoes for up to four weeks (a [one] month).

STUDY REVIEW

Purpose: To review the efficacy data for Effitix™ Topical Solution for Dogs against fleas, ticks, mites, lice, mosquitoes, biting flies and sand flies.

BACKGROUND

Effitix™ Topical Solution for Dogs contains two active ingredients: 6.01% w/w fipronil and 44.88% w/w permethrin. The registrant proposes using three types of efficacy data in support of its application for registration of Effitix™ Topical Solution for Dogs: 1) data previously submitted, reviewed and accepted by the Agency for fipronil spot on products and for certain permethrin spot-on products; 2) data published in the open literature on certain permethrin spot on products; and 3) new efficacy studies using Effitix™ Topical Solution for Dogs (MRID numbers were not provided for these studies).

NOTE: In MRID 484671-29 the registrant does not present any of the quantitative data given in the previously submitted and accepted MRIDS for fipronil and permethrin. The published information on permethrin is discussed briefly and copies of the published articles are included in an Appendix to MRID 484671-29. Studies conducted on Effitix™ Topical Solution for Dogs are summarized in MRID 484671-29 in a condensed format.

RESULTS

Data on Efficacy Against Fleas

Data on the efficacy of Effitix™ Topical Solution against fleas on dogs is summarized in Table 1.

Table 1. Summary of Efficacy Data for Effitix™ Topical Solution Against Fleas on Dogs

Test Species	Citation	Result
Cat flea *(Ctenocephalides felis)*	Fourie, J.J. 2009. Efficacy Study Against Fleas (*Ctenocephalides felis*) on Dogs: Onset of Action. December 9, 2009.	Kills >90% of fleas within 6 hr and >99% within 12 hr
Cat Flea *(Ctenocephalides felis)*	Fourie, J.J. 2009. Efficacy Study Against the Brown Dog Tick (*Rhipicephalus sanguineus*) and the Cat Flea *(Ctenocephalides felis)* on Dogs: Effects of Shampooing and Periodic Water Immersions.	The use of shampoo or water immersion had no effect on the efficacy of the product; efficacies were 100% after shampooing and

		water immersions.

Data on the efficacy of permethrin against fleas in dogs are summarized in Tables 2 and 3. Data on the efficacy of fipronil against fleas in dogs are summarized in Table 4.

Table 2. Published Data on the Efficacy of Permethrin Against Fleas

EPA Reg. #	Publication	MRID #
773-73	Endris, R. *et al*: Efficacy of two 65% permethrin spot-on formulations against induced infestations of Ctenocephalides felis (Insecta: Siphonaptera) and Amblyomma americanum (Acari: Ixodidae) on beagles. Vet Ther. Spring 2003;4(1):47-55	unknown
773-73	Endris, R. *et al*: Efficacy of three dose volumes of topically applied 65% permethrin against Ctenocephalides felis and Rhipicephalus sanguineus on dogs weighing 30 kg or more. Vet Ther. Winter 2002;3(4):435-40	unknown
773-73	Endris, R. *et al*: Efficacy of two 65 % permethrin spot-on formulations against canine infestations of Ctenocephalides felis and Rhipicephalus sanguineus. Vet Ther. Fall 2002;3(3):326-33	unknown
270-278-43591	Ross, D. *et al*: Efficacy of a permethrin and pyriproxyfen product for control of fleas, ticks and mosquitoes on dogs. Canine Pract. 1997; 22(2):53-58	46006002
Not applicable	Tilley L.P. and Smith W.K.: Tularemia in Blackwell's five-minute veterinary consult: canine and feline, fourth edition, 2007 Blackwell Publishing Professional, p.1365.	Unknown

Table 3. Unpublished Data on the Efficacy of Permethrin Against Fleas

Guideline		MRID #	Claim
810.3300		41038802	Fleas
810.3300		41038803	Fleas
810.3300		43137202	Fleas
810.3300		43137203	Fleas
810.3300		43396409	Fleas
810.3300		43396410	Fleas

Table 4. Unpublished Data on the Efficacy of Fipronil Against Fleas

Guideline	MRID #	Claim
810.3300	43121114	Fleas
810.3300	43121115	Fleas
810.3300	43121116	Fleas
810.3300	43121119	Fleas
810.3300	43121120	Fleas
810.3300	43121121	Fleas
810.3300	43121122	Fleas
810.3300	43444901	Fleas
810.3300	43577701	Fleas
810.3300	43577712	Fleas
810.3300	43577713	Fleas
810.3300	43951701	Fleas
810.3300	44088901	Fleas
810.3300	44942011	Fleas
810.3300	44942106	Fleas
810.3300	45618501	Fleas
810.3300	45620502	Fleas
810.3300	45620503	Fleas
810.3300	45628104	Fleas
810.3300	45628105	Fleas
810.3300	45866901	Fleas

Data on Efficacy Against Ticks

Data on the efficacy of Effitix™ Topical Solution against ticks on dogs are summarized in Table 5.

Table 5. Summary of Efficacy of Effitix™ Topical Solution Against ticks in Dogs

Test Species	Citation	Result
Brown dog tick *(Rhipicephalus sanguineus)*	Fourie J.J. 2009. Efficacy Study Against *Rhipicephalus sanguineus* in Dogs: Duration of Action.	The duration of >90% efficacy was 7 weeks
American dog tick, *(Dermacentor variabilis)*	Fourie, J.J. 2009. Efficacy Study Against *Dermacentor variabilis* on Dogs: Duration of Action.	The duration of efficacy was 6 weeks
Lone star tick, *(Amblyoma americanum)*	Moran, C. 2010. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%, Permethrin 50%) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Amblyoma americanum*) on Dogs.	The duration of efficacy was between 4 and 5 weeks
Deer tick *(Ixodes scapularis)*	Moran, C. 2010. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%w/v, Permethrin 50% w/v) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Ixodes scapularis*) on Dogs.	The duration of efficacy was at least 5 weeks
Dog ticks, (*D. variablis and R. sanguineus)*	Fourie, J.J. 2010. Repellence Efficacy Study of 104.05 Against Ticks (*Dermacentor variabilis* and *Rhipicephalus songuineus*) on Dogs Under Laboratory Conditions. November 3, 2010.	Effective for at least one month. 24-hr efficacy against *R. sanguineus* was 100% on day 4, 99% on day 9 and 100% on all other days; 24 hr efficacy against *D. variabilis* was 97.6% on day 2, 100% on day 4, and ≥97.7% on all other days

Brown Dog Tick (*R. sanguineus)*	Fourie, J.J. 2009. Efficacy Study Against the Brown Dog Tick (*Rhipicephalus sanguineus*) and the cat Flea *(Ctenocephalides felis)* on Dogs: Effects of Shampooing and Periodic Water Immersions.	The use of shamopoo or water immersion had no effect on the efficacy of the product; efficacies were ≥99.5% after shampooing and after water immersions.

Data on the efficacy of permethrin against ticks in dogs are summarized in Tables 5 and 6. Data on the efficacy of fipronil against ticks in dogs are summarized in Table 7.

Table 5. Published Data on the Efficacy of Permethrin Against Ticks

EPA Reg. #	Publication	MRID #
773-73	Endris, R. *et al*: Efficacy of two 65% permethrin spot-on formulations against induced infestations of Ctenocephalides felis (Insecta: Siphonaptera) and Amblyomma americanum (Acari: Ixodidae) on beagles. Vet Ther. Spring 2003;4(1):47-55	Unknown
773-73	Endris, R. *et al*: Efficacy of three dose volumes of topically applied 65% permethrin against Ctenocephalides felis and Rhipicephalus sanguineus on dogs weighing 30 kg or more. Vet Ther. Winter 2002;3(4):435-40	Unknown
773-73	Endris, R. *et al*: Efficacy of two 65 % permethrin spot-on formulations against canine infestations of Ctenocephalides felis and Rhipicephalus sanguineus. Vet Ther. Fall 2002;3(3):326-33	Unknown
270-278-43591	Ross, D. *et al*: Efficacy of a permethrin and pyriproxyfen product for control of fleas, ticks and mosquitoes on dogs. Canine Pract. 1997; 22(2):53-58	46006002
773-73	Endris, R. *et al*: Repellency and efficacy of 65% permethrin and selamectin spot-on formulations against *Ixodes ricinus* ticks on dogs. Vet Ther. Spring 2002;3(1):64-71	Unknown

Table 6. Unpublished Data on the Efficacy of Permethrin Against Ticks

Guideline	MRID #	Claim
810.3300	41683903	Ticks
810.3300	43111607	Ticks
810.3300	43396409	Ticks
810.3300	43396410	Ticks

Table 7. Unpublished Data on the Efficacy of Fipronil Against Ticks

Guideline	MRID #	Claim
810.3300	43577712	Ticks
810.3300	43121114	Ticks
810.3300	43121115	Ticks
810.3300	43121117	Ticks
810.3300	43121122	Ticks

Data on Efficacy Against Mosquitoes

Data on the efficacy of Effitix™ Topical Solution against mosquitoes on dogs are summarized in Table 8.

Table 8. Summary of Efficacy Information for Effitix™ Topical Solution Against Mosquitoes in Dogs

Test Species	Citation	Result
Mosquito (*Aedes aegypti*)	Monzali, C. 2011. Determination of a Combination of Fipronil and Permethrin in Topical Solution Against Mosquitoes (*Aedes aegypti*) on Dogs	Anti-feeding efficacy on short hair dogs ranged from 52.5% on day 35/37 to 96.2% on day 7. Anti-feeding efficacy on long hair dogs ranged from -156.7% on day 35/37 to 84.5% on day 21/22. Killing efficacies were 50-60% up to day 21 in short hair dogs, and <12% up to day 28 in long hair dogs.

Data on the efficacy of permethrin against mosquitoes in dogs are summarized in Tables 9 and 10. Data on the efficacy of fipronil against mosquitoes in dogs are summarized in Table 11.

Table 9. Published Data on the Efficacy of Permethrin Against Mosquitoes

EPA Reg. #	Publication	MRID #
773-73	Meyer *et al.*: Repellency and Efficacy of a 65 % Permethrin Spot-on Formulation for dogs against *Aedes aegypti* (Diptera: Culicidae) Mosquitoes. Vet Ther. Summer 2003;4(2):135-143.	Unknown
270-278-43591	Ross, D. et al: Efficacy of a permethrin and pyriproxyfen product for control of fleas, ticks and mosquitoes on dogs. Canine Pract. 1997; 22(2):53-58	46006002

Table 10. Unpublished Data on the Efficacy of Permethrin Against Mosquitoes

Guideline	EPA Reg. #	MRID #	Claims supported
810.3300	773-73	42256901	Kills and repel mosquitoes (4 weeks)
810.3300		43396409	
810.3300		43396410	

Table 11. Unpublished Data on the Efficacy of Fipronil Against Mosquitoes

Guideline	MRID #	Claim
810.3300	45866902	Mosquitoes
810.3300	46019202	Mosquitoes
810.3300	46019201	Mosquitoes

Data on Efficacy Against Mites

Data on the efficacy of Effitix™ Topical Solution against mites on dogs are not available. Permethrin data are summarized in Table 12, fipronil data in Table 13.

Table 12. Published Data on the Efficacy of Permethrin Against Mites

EPA Reg. #	Publication	MRID #
773-73	Endris *et al.*: Efficacy of 65 % Permethrin Applied as a Topical Spot-on Against Walking Dandruff Caused by the Mite, Cheyletiella yasguri in Dogs. Vet Ther. Fall 2000;1(4):273-279	Unknown

Table 13. Unpublished Data on the Efficacy of Fipronil Against Mites

810.3300	43577701	Mites
810.3300	43951701	Mites
810.3300	45612701	Mites
810.3300	45620503	Mites
810.3300	45866901	Mites

Data on Efficacy Against Lice

Data on the efficacy of Effitix™ Topical Solution against lice on dogs are not available. Permethrin data are summarized in Table 14; fipronil data in Table 15.

Table 14. Published Data on the Efficacy of Permethrin Against Lice

EPA Reg. #	Publication	MRID #
773-73	Endris *et al.*: Efficacy of a Topical Spot-on containing 65 % Permethrin against the Dog Louse *Trichodectes canis* (Mallophaga: Trichodectidae). Vet Ther. Spring 2001;2(2):135-139.	Unknown

Table 15. Unpublished Data on the Efficacy of Fipronil Against Mites

Guideline	MRID #	Claim
810.3300	45620501	Lice
810.3300	45628101	Lice
810.3300	45628102	Lice
810.3300	45628103	Lice
810.3300	45628201	Lice

Data on Efficacy Against Biting Flies

Data on the efficacy of Effitix™ Topical Solution against biting flies on dogs are not available. Permethrin data are summarized in Table 16; there are no data for fipronil.

Table 16. Unpublished Data on the Efficacy of Permethrin Against Biting Flies

Guideline	EPA Reg. #	MRID #	Claims supported
810.3300	11556-132, 133, 134, 135	46978901 (2004)	Repels biting flies for three weeks

Data on Efficacy Against Sandflies

Data on the efficacy of Effitix™ Topical Solution against sandflies on dogs are not available. Permethrin data are summarized in Table 17; there are no data for fipronil.

Table 17. Published Data on the Efficacy of Fipronil Against Sand Flies

EPA Reg. #	Publication	MRID #
773-73	Molina *et al.*: Evaluation of a topical solution containing 65 % Permethrin against the Sandfly (*Phlebotomus perniciosus*) in Dogs. Vet Ther. Summer 2001;2(3):261-267.	

Study Author's Conclusions

The study author's conclusions are presented in Table 18.

Table 18. Summary of Data Available on the Efficacy of Effitix™ Topical Solution, Permethrin and Fipronil Against Target Organisms on Dogs

Fleas (*C. felis*)	Repels and kills fleas for up to three months Repel and kills fleas in six hours
Ticks (*R. sanguineus, A. americanum, I. scapularis, I. ricinus, D. variabilis*)	Repels and kills ticks for at least one month Kills 90% of the ticks in 3 hours
Lice	Kills and repels *Trichadectes canis* for up to 4 weeks Kills sucking, biting and chewing lice for a month or longer
Mites (*C. yasguri, S. scabiei* var *canis*)	Kills mites (*C. yasguri*) for up to four weeks Aids in the control of sarcoptic mange mite infestation
Mosquitoes (*A. aegypti*)	Prevents blood feeding, kills, repels mosquitoes for up to one month
Biting flies (*S. calcitrans*)	Prevents blood feeding and repels biting flies for up to three weeks
Sandflies (*P. perniciosus*)	Prevents blood feeding and repels sand flies for up to one month

Reviewer's Conclusions

Information on the efficacy on Effitix™ Topical Solution for Dogs was adequately reviewed. Although the use of permethrin and fipronil efficacy data in support of the registration of Effitix™ Topical Solution for Dogs is justified, the information provided was inadequate. It could not always be determined if the dose rates used in the previously accepted studies were less than or equal to the dose rates proposed for Effitix™ Topical Solution for Dogs. Furthermore, the use of data from products that contain more than one active ingredient was not always clearly justified. For example, data for K9 Advantix is used to support biting fly claims for Effitix™ Topical Solution; however, the presence of imidacloprid in the product, in addition to permethrin, may have affected the results (although the author of MRID 484671-29 claims that imidacloprid "is not itself effective on biting flies"). Study author uses data for a 65% permethrin product to support claims of efficacy against sandflies, and states that the dose rate by kg or lb is equal to or below that for Effitix™ Topical Solution; however, no quantitative data were presented to support this claim.

Reviewer's Recommendations

Unacceptable, but upgradable. The reviewer did not have access to information needed for the supporting permethrin and fipronil studies on lice, mites and biting flies. Sandflies are not listed on the label.

Virbac - 2382-RIT
Wade Britton
to:
jbarron
11/07/2011 07:13 PM
Cc:
brenton.smith, Kimberly Nesci, Richard Gebken, Bonaventure Akinlosotu
Hide Details
From: Wade Britton/DC/USEPA/US

To: jbarron@exponent.com

Cc: brenton.smith@virbacus.com, Kimberly Nesci/DC/USEPA/US@EPA, Richard Gebken/DC/USEPA/US@EPA, Bonaventure Akinlosotu/DC/USEPA/US@EPA

1 Attachment

Image.image001.jpg@01CC97B3.3764E100.PLAIN

Mr. Barron - I am writing in confirmation of our discussion this morning regarding Virbac's pending registration, 2382-RIT. Due to the short time frame from the mailing of the letter outlining the recommended label changes to the November 19, 2011 PRIA date for the pending registration, the Agency will not be requiring that these changes be addressed prior to product registration. However, please note that EPA does anticipate the submission of amended labeling incorporating the recommended changes within 6 months following product registration.

We are continuing to consider the specific questions/rationale provided by Virbac following our Oct 13, 2011 meeting.

Best Regards, Wade

~ * ~ * ~ * ~ * ~ * ~ * ~ * ~ * ~ * ~ * ~ * ~ * ~ * ~
Wade Britton, MPH
Industrial Hygienist; Health Effects Division
Office of Pesticide Programs, US EPA
(703)308-0139

-----"Jim Barron" <jbarron@exponent.com> wrote: -----

> To: Wade Britton/DC/USEPA/US@EPA
> From: "Jim Barron" <jbarron@exponent.com>

Date: 10/31/2011 09:54AM
Cc: "Brenton Smith" <brenton.smith@virbacus.com>
Subject: 2382-RIT

Wade,

Hope you had a good weekend. Any decision taken by your team on our proposed labeling for Effitix topical solution for dogs.? Also, did you receive the proposed printed labeling which we had sent to Bonaventure and Richard Gepken?

Thanks for your help.

Jim Barron, Ph. D.

Managing Regulatory Consultant

Exponent®, Inc.

1000 Centre Green Way Suite 200

Cary, NC 27513

Office Telephone (919) 228-6479

Mobile Telephone (919) 534-6018

Facsimile (919) 228-6501

Email Address jbarron@exponent.com

in error, please destroy it immediately and notify the sender by telephone. Thank you

********** ATTACHMENT NOT DELIVERED
****

This Email message contained an attachment named
image001.jpg
which may be a computer program. This attached computer program could
contain a computer virus which could cause harm to EPA's computers, network, and data. The attachment has been deleted.

This was done to limit the distribution of computer viruses introduced
into the EPA network. EPA is deleting all computer program attachments
sent from the Internet into the agency via Email.

If the message sender is known and the attachment was legitimate, you
should contact the sender and request that they rename the file name extension and resend the Email with the renamed attachment. After receiving the revised Email, containing the renamed attachment, you can
rename the file extension to its correct name.

For further information, please contact the EPA Call Center at (866) 411-4EPA (4372). The TDD number is (866) 489-4900.

********** ATTACHMENT NOT DELIVERED
****

Effitix- CRP questions
Jim Barron
to:
Bonaventure Akinlosotu
11/03/2011 11:19 AM
Cc:
melissa.lum, "Brenton Smith"
Hide Details
From: "Jim Barron" <jbarron@exponent.com>

To: Bonaventure Akinlosotu/DC/USEPA/US@EPA

Cc: <melissa.lum@virbacus.com>, "Brenton Smith" <brenton.smith@virbacus.com>

1 Attachment

image003.jpg

Bonaventure,

Rosalind and I have this morning discussed by phone her concerns about the proposed Effitix text label (6-21-11) version as well as the mock-up artwork label we submitted 10-5-11.

Bonaventure, I believe that Rosaling will be talking to you and summarizing the actions for you. My main action is to provide you with revised text labeling where we have moved the bullets describing proposed illustrations that now appear on page 4 to the end of the "Marketing Claims" sections on page 9. This is the location where we listed the proposed illustrations on the now approved Effipro label (2382-185). Addressing the last bullet statement in that group (the bullet that proposes an illustration of the applicator tube), Virbac will also either provide a proposed picture of the applicator tube or we will strike that statement for now. I have to obtain confirmation from Virbac first on that mattern.

The only other CRP related question that Rosalind and I discussed and which you and I should touch base on now is the incorrect arrow placement on opening instructions that Rosalind noticed in the mock up draft artwork label submitted 10-5-11. My suggestion is to handle this by instructing Virbac in the NOR to make sure that those opening instruction diagrams (especially the arrows) in the final printed labeling (artwork) are drawn identically to the opening instructions in the text label that you will stamp.

If you need to discuss this with me further, let me know.

I am back in the office. The phone number is 919 462-9860.

Thanks,

Jim Barron, Ph. D.
Managing Regulatory Consultant
E^xponent®, Inc.
1000 Centre Green Way Suite 200
Cary, NC 27513

Office Telephone (919) 228-6479
Mobile Telephone (919) 534-6018
Facsimile (919) 228-6501
Email Address jbarron@exponent.com

Virbac
ANIMAL HEALTH

October 5, 2011

Bonaventure Akinlosotu, PM Team 10
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Document Processing Desk
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Subject: Effitix® Topical Solution for Dogs (EPA Reg. No 2382-RIT); Proposed Labeling.

Dear Bonaventure,

Please find enclosed proposed printed labeling for Effitix (2382-RIT) for referencing during our October 13 teleconference.

In addition, here are Virbac questions/comments resulting from the September 30, 2011 Lois Rossi Letter that the company would like to discuss during the teleconference:

In order of importance:

1. We do not believe it should be necessary to add the phrase - "MAY BE FATAL".

2. We do not want to increase the size of the word "Dogs" for the product name. The word "Dogs" is stated at least 12 times on the one-pack alone, so we feel that this should be very clear on this package. Increasing the font size would require us to remove other important information from the package. This is an even greater issue with the request to increase the size of the "cat prohibition icon".

3. We do not think it should be necessary to place a 'cat prohibition' icon in the lower right hand corner - we feel we already have this icon multiple places throughout the packaging (front panel, back panel, package insert, blister and pipette). We consider the placement of the icon closer to the middle of the package to be better in terms of visibility for the pet owner.

3200 Meacham Blvd. • Fort Worth, TX 76137 Telephone: (817) 831-5030 • (800) 338-3659 Fax (817) 831-8327

Virbac
ANIMAL HEALTH

4. Increasing the size of the cat icon to 1.5 cm x 1.5 cm is a reasonable request on the larger package presentations (3, 6 and 36-packs) because there is more room to meet these dimensions. However, on the one-pack this will be very hard to accommodate. We also believe that there is an inherently lower need for this adjustment based on the one use nature of a one-pack, which we do not expect pet owners to take home and store for future use. We feel there shouldn't be any confusion about which pet these products in the one-pack should be applied to.

5. Changing the colors of the "cat prohibition icon". The colors were chosen to stand out against the background colors of the different packages. We believe the presence of this icon is in enough places that there shouldn't be any confusion (front panel, back panel, package insert, blister and pipette).

6. "Keep cats away from treated dogs for 24 hours"- This seems to only be a necessary warning for 'Keep cats that groom dogs away'. This should be more specific as this is a very rare issue.

7. Expanding the toxicity warnings to be broken down by active ingredient is a concern based on the amount of space that this would require. The listing of side effects is complete based on the total product so this duplicated effort would negatively impact the amount of space for other warnings that are necessary for these packages.

We look forward to discussing these questions with you during the October 13, 2011 teleconference.

Sincerely,

Brenton Smith /MST

Brenton Smith, Ph.D, PMP
Product Development Manager
Research and Development

3200 Meacham Blvd. • Fort Worth, TX 76137 Telephone: (817) 831-5030 • (800) 338-3659 Fax (817) 831-8327

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

DP BARCODE No.: D390814 FILE SYMBOL No.: 2382-RIT DECISION No.: 448350
PC CODES: 109701, 129121 ACTION CODE: R 310
FOOD USE: No PRODUCT NAME: Effitix Topical Solution for Dogs

DATE OUT: October 25, 2011

SUBJECT: End Use Product Chemistry Review
Product Name: Effitix Topical Solution for Dogs

FROM: Bruce F. Kitchens, Chemist
Product Chemistry Team
Technical Review Branch/RD (7505P)

Bruce F. Kitchens
25 Oct 2011

TO: RM 10, Richard Gebken/Bonaventure Akinlosotu
Insecticide Branch / RD (7505P)

SBun 10/26/11

Company Name: Virbac AH, Incorporated
Formulation Type: Liquid

INTRODUCTION:

The registrant has submitted an application for the registration of the new end use product, Effitix Topical Solution for Dogs. The active ingredients in this product are Fipronil and Permethrin at label nominal concentrations of 6.01 and 44.88% a.i., respectively. The fipronil source is not registered. This product is intended for use as a topical insecticide for dogs. In support of the registration application, the registrant has submitted a Confidential Statement of Formula (CSF) dated 21 Mar 2011, a draft label and 830 Series Group A and B product chemistry data contained in MRID#s 484671-01, -02, -03, -04, -05, -06, -07, -08, -10 and 484873-01. During the course of this review, the registrant submitted a revised basic CSF dated 21 Oct 2011 to correct a calculation. The Technical Review Branch (TRB) has been asked to review this submission.

SUMMARY OF FINDINGS:

1. Name of Active Ingredients: Fipronil (6.01% a.i.)
Permethrin (44.88% a.i.)

2. Has the registrant claimed substantial similarity to a registered product?

[ ] Yes; [X] No

3. All of the source materials of the active ingredient are derived from registered sources- [ ] Yes [X] No

The fipronil source of the active ingredient is not registered. The purity of the unregistered source is [redacted] as stated by the registrant.

4. All inert ingredients have been screened by IIAB and found to be approved for the proposed labeled uses.

DP BARCODE No.: D390814 FILE SYMBOL No.: 2382-RIT DECISION No.: 448350
PC CODES: 109701, 129121 ACTION CODE: R 310
FOOD USE: No PRODUCT NAME: Effitix Topical Solution for Dogs

5. Confidential Statement of Formula:

[X[Basic - Dated: 21 Mar 2011 ; Re-submitted - Dated: 21 Oct 2011

6. Product label

a. Ingredient statement: Nominal concentration of AI listed on CSF concurs with product label (PR Notice 91-2).
[X[Yes, if not, explain below:

Is the sub statement in compliance with PR Notice 97-6 (inert ingredient vs other ingredient)
[X[Yes; [ ] No; if not, explain below

Metallic equivalent: [[Yes [X] NA;
Soluble arsenic: [ ) Yes [X] NA
Isomeric ratios: [X[Yes [ ] NA Permethrin cis/trans ratio: max 55% (±) cis & min 45%(±) trans
Acid Equivalent: [ ] Yes [X] NA

b. Health related sub statements: Product contains?

Petroleum distillate at > 10%: [[Yes; [[No; [X[NA
Methanol at > 4%: [[Yes; [[No; [X[NA
Sodium nitrate/sodium nitrite [[Yes; [[No; [X] NA

c. Physical chemical hazard statement: Product label requires a statement per 40 CFR §156.78 for: flammability, explosive potential or electric insulator breakdown?
[ ] Yes [X[No

Is the sub statement in compliance with PR Notice 98-6 (Total Release Fogger)?
[[Yes; [[No; [X[NA; if not, explain below

d. Label requires an additional Storage and Disposal statement: [[Yes [X] No; if yes explain below:

7. Group **A**: Product Chemistry Data

TRB's determination of the acceptability for the proposed product is listed in the tables below.

Guideline No.	Study Title		Data submitted		TRB's Assessment of Data	MRID Nos.
			Yes	No		
830.1550	Product Identity & Composition		X		A	484671-01
830.1600	Description of Materials Used to Produce the Product		X		A	484671-01
830.1650	Description of Formulation Process		X		A	484671-01
830.1670	Discussion of the Formation of Impurities		X		A	484671-01
830.1700	Preliminary Analysis		X		A	484671-02
830.1750	Certified limits (158.350)	Standard Certified Limits	X			see csf 10/21/11
		Proposed Limits				
		Justification for wider limits				
830.1800	Enforcement Analytical Method		X		A	484671-03

A = Acceptance, N = Not Acceptable, G = Data Gap, W = Waiver Request, I = In Progress, NA = Not Applicable; U = Upgradeable.

8. Group **B:**

Guideline No.	Study Title	Value or Qualitative Description	TRB's Assessment of Data	MRID Nos.
830.6303	Physical State	Yellow odorless liquid	A	484671-04
830.6315	Flammability	96.28°C (flash point)	A	484671-06
830.6316	Explodability	Product does not have explosive components	NA	
830.7000	pH	5.30 @ 22°C	A	484671-08
830.7300	Density (units)	1.114 (relative density)	A	484671-10

A = Acceptance, N = Not Acceptable, G = Data Gap, W = Waiver request, NA = Not applicable, I = In progress; U = Upgradeable.

9. The registrant referenced product chemistry data for the unregistered source of fipronil. This source is a component of EPA Reg. Nos. 2382-185 Effipro Topical Solution for Dogs and 2382-186 Effipro Topical Solution for Cats. The stated purity of the unregistered source is [redacted] The producer of the unregistered source used in this proposed product is the same as the producer for the registered end-use products mentioned above. This data was reviewed and it was determined that the data was acceptable and supported the registrations for the currently registered end-use products. See the confidential appendix for a summary of the product chemistry data requirements for the unregistered source of the active ingredient fipronil.

Product ingredient source information may be entitled to confidential treatment

DP BARCODE No.: D390814 FILE SYMBOL No.: 2382-RIT DECISION No.: 448350
PC CODES: 109701, 129121 ACTION CODE: R 310
FOOD USE: No PRODUCT NAME: Effitix Topical Solution for Dogs

CONCLUSIONS:

The TRB has reviewed the product chemistry data submitted for the proposed end-use product and has concluded that:

1. The basic formula CSF for the proposed end-use product, Effitix Topical Solution for Dogs dated 21 Oct 2011 is acceptable.

2. This submission satisfies the data requirements as specified in 40 CFR 158.155, 158.160, 158.165, 158.167, 158.175, and 158.180 with respect to product identity and composition, description of materials used to produce the product, description of formulation process, discussion of formation of impurities, certified limits, and enforcement analytical method.

3. This submission satisfies the data requirements as specified in 40 CFR 158.190 with respect to physical and chemical properties.

DP BARCODE No.: D390814 FILE SYMBOL No.: 2382-RIT DECISION No.: 448350
PC CODES: 109701, 129121 ACTION CODE: R 310
FOOD USE: No PRODUCT NAME: Effitix Topical Solution for Dogs

CONFIDENTIAL APPENDIX

The product chemistry data submitted for the unregistered source of fipronil is summarized in the following tables.

COMMON NAME: Fipronil

CHEMICAL NAME (CAS): 1H-Pyrazole-3-carbonitrile, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-

(IUPAC): 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(1,R,S)-(trifluoromethylsulfinyl)-1H-pyrazole-3-carbonitrile

CAS No.: 120068-37-3

PC CODE NO.: 129121

EMPIRICAL FORMULA: $C_{12}H_4Cl_2F_6N_4OS$

MOLECULAR WEIGHT: 437.15

STRUCTURAL FORMULA:

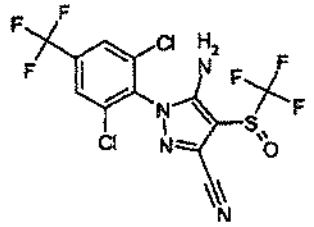

TABLE 1. Manufacturing and Impurity Data for TGAI/MUP

GLN	Requirement	MRID	Status	Details and /or Deficiency
830.1550	Product identity and composition	480952-40	A	Product label will need to be reviewed (not available to the reviewer)
8301600	Description of materials used to produce the product	480952-39	A	See confidential appendix. Additional MSDS's have been submitted (11-02-10)
830.1620	Description of production process	480952-39	A	
830.1670	Discussion of formation of impurities	480952-40	A	
830.1700	Preliminary analysis	480952-41	A	
810.1750	Certified limits	480952-40	A	See confidential appendix
830.1800	Enforcement analytical method	480952-42 482837-03	A	

A = Acceptable; N = unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress or need upgrade; U = Up-grade (additional information required)

DP BARCODE No.: D390814 FILE SYMBOL No.: 2382-RIT DECISION No.: 448350
PC CODES: 109701, 129121 ACTION CODE: R 310
FOOD USE: No PRODUCT NAME: Effitix Topical Solution for Dogs

CONFIDENTIAL APPENDIX:

830 Series Subgroup B (Physical-Chemical Properties)

Table 2: Physical and Chemical Properties of : TGAI/MUP

GLN	Requirement	MRID	Status	Result or Deficiency
830.6302	Color	480952-40	A	White
830.6303	Physical state	480952-40	A	Crystalline powder
830.6304	Odor		NA	
830 6313	Stability to normal and elevated temperatures, metals, and metal ions	Letter dated 11-02-10	W	Waiver accepted
830.6314	Oxidation/reduction: chemical incompatibility	480952-39	A	Incompatible with strong bases, strong acids, and strong oxidizing agents
830.6315	Flammability	480952-39	A	Not flammable
830.6316	Explodability	480952-39	A	Not explosive
830.6317	Storage stability	480952-43	U	Stable after 14 days at 54°C
830.6319	Miscibility		N/A	Not intended to be mixed with petroleum solvents
830.6320	Corrosion characteristics		G	No data provided
830.7000	pH	480952-47	A	6.05 at 22°C
830.7050	UV/Visible absorption	480952-48	A	UV/VIS spectra were very similar at pH 0.6, pH 6.7, and pH 13.2
830.7100	Viscosity		N/A	Product is a solid
830.7200	Melting point	480952-49	A	203.9± 0.1°C
830.7220	Boiling point		N/A	Product is a solid
830.7300	Density	480952-50	A	D_4^{20}= 1.716
830.7370	Dissociation constants in water (DC)	480952-51	W	Not an acid, has no organic functionality; no dissociation is expected
830.7550	Partition coefficient	480952-44	A	Log Paw = 2.96
830.7840	Water solubility	480952-45	A	1.59 mg/L at 20°C
830.7950	Vapor pressure	48095246	A	1.0×10^{-6} at 25°C 2.0×10^{-3} Pa at 80°C 2.5×10^{-2} Pa at 100°C 4.8×10^{-2} Pa as 110°C

? Bk ✓ Bruce NR

A = Acceptable; N = unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress or need upgrade; U = Up-grade (additional information required); W = waivers

DP BARCODE No.: D390814
PC CODES: 109701, 129121
FOOD USE: No

FILE SYMBOL No.: 2382-RIT
ACTION CODE: R 310
PRODUCT NAME: Effitix Topical Solution for Dogs

DECISION No.: 448350

CONFIDENTIAL APPENDIX:

Chemical	Fipronil	Registration No.	2382-???	DP Barcode	D379877
CB Number	?	Product Type	Insecticide	Test Substance	TGAI/MUP

Group A-GLNS 830.1550, 830.1600, 830.1620, 830.1650, 830.1670, 830.1700, 830.1750, & 830.1800: Composition (CSF), Impurities, Preliminary analysis, and Analytical Methods

Compound/Component			Nominal Concentration (% w/w)	Lower Certified limit concentration (% w/w)	Upper Certified limit concentration (% w/w)	Preliminary Analysis Mean ± s. d. (% w/w)
No	Name	Type				
	Fipronil CAS No. 120068-37-3	AI	[redacted]			

[redacted]

Manufacturing process information may be entitled to confidential treatment

CHEMICAL NAME/PESTICIDE CHEMICAL CODE (PCC) REQUEST FORM

CR# _____

REQUESTOR NAME: Bruce Kitchens			Request date: 24 Oct 2011
Tel: 308-9312	ORG.: RD/TRB	CUBE: S-7331	MAIL CODE: 7505P

CSF ATTACHED:
[X] YES If CSF is attached complete Item A and the chemical name in item C.
[ ] NO If CSF is not attached complete Item A through C.

A. INFORMATION REQUIRED:

Check Applicable Category

[ ] Provide PCC and Tolerance Exemption Status For Food-Use Inert ingredient (s).
[X] Provide PCC for Non-Food Use inert Ingredient (s).
[ ] Provide PCC for Active Ingredient (s).
[ ] Provide PCC for Dye.
[ ] Determine if Fragrance is Acceptable for Use In Formulation.
[ ] *Other (Describe):* _____

B. PESTICIDE PRODUCT INFORMATION:

EPA Reg. No/File Symbol: VIRBAC AH, INC.	Product Name: Effitix Topical Solution for Dogs
Registrant: 2382 - RIT	Food-Use Pesticide: [ ] Yes [X] No
Percent in Formulation (For Fragrance /Dyes)	

C. INGREDIENT INFORMATION:

Ingredient No.1 **INFORMATION REPORTED:**

Chem. Name:	PCC: ~
Trade Name:	TOL. STATUS:
CAS Reg. No.:	OTHER INF.:

Ingredient No.2:

Chem. Name:	PCC:
Trade Name:	TOL. STATUS:
CAS Reg. No.:	OTHER INF.:

Ingredient No.3

Chem. Name:	PCC:
Trade Name:	TOL. STATUS:
CAS Reg. No.:	OTHER INF.:

Ingredient No.4:

Chem. Name:	PCC:
Trade Name:	TOL. STATUS:
CAS Reg. No.:	OTHER INF.:

Completed By: D. Rod
Date Completed: 10/25/11

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

October 13, 2011

MEMORANDUM

Subject:	Name of Pesticide Product:	EFFITIX™ TOPICAL SOLUTION FOR DOGS
	EPA Reg. No. /File Symbol:	2382-RIT
	DP Barcode:	DP 390818
	Decision No.:	448350
	Action Code:	R310
	PC Code:	109701 (Permethrin: 44.88%)
		129121 (Fipronil: 6.01%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus October 13, 2011

M Hawkins Ph.D. Lead Toxicologist

To: Bonaventure Akinlosotu/Richard Gebken, RM 10
Insecticide Branch
Registration Division (7505P)

Registrant: VIRBAC AH, INC.

FORMULATION FROM LABEL:

Active Ingredient(s):		by wt.
129121 Fipronil		6.01%
109701 Permethrin		44.88%
Other Ingredients:		49.11%
	TOTAL	100.00%

ACTION REQUESTED: The Risk Manager requests:

"For your review: MRID Nos. 484671-17 to 20, and 48487302; for an R310, new fipronil/permethrin containing spot-on for dogs…"

BACKGROUND:

The material received includes three companion animal safety studies: MRID 48467117 (a companion animal safety study in adult beagles); MRID 48467118 (a companion animal safety study in approximately 8 week old beagles); and MRID 48487302 (a second companion animal safety study in approximately 8 week old beagles). There is also a report (in MRID 48467119) titled "Summary of Companion Animal Safety Data for Effitex™. In addition, there is a proposed label (indicating a dose rate of 1.0 mL for small dogs and puppies 8 weeks of age and older weighing up to 22.9 lbs; 2.0 mL for dogs weighing between 23 and 44.9 lbs; 4.0 mL for dogs weighing between 45 and 88.9 lbs; and 6.0 mL for dogs weighing between 89 and 132 lbs) with application at 30-day intervals.

COMMENTS AND RECOMMENDATIONS:

1. The three companion animal safety studies were reviewed by a contractor (Summitec Corporation). The resulting DERs were secondarily reviewed by TRB and revisions were made as appropriate.

2. In the study in adult beagles (MRID 48467117) it is concluded that the margin of safety in 10- to 20-kg adult beagle dogs administered 104.05 [End-use Product: Effitix™ Topical Solution for Dogs] is at least 5x the recommended dose (2.0 mL/dog). This companion animal safety study in dogs is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in adult dogs.

3. In a study with 8 week old beagle puppies (MRID 48467118) effects were seen that were dose-related. At the 5X dose level there were increased incidences of vomiting and abnormal feces, i.e. feces that were liquid, loose, mucoid, with traces of blood, and/or discolored (seen in 4-5 5X animals vs. 0 controls). The 5X animals of both sexes had decreased weight gain during days -1 to 7 (51% and 55% less than controls for males and females, respectively). During days 1-5 of the study, the daily food consumption of the 5X animals was 32-50% less than that of controls ($p<0.01$), and there were 26 occasions (involving nine 5X puppies) in the period from Day 1 to 9 when a 5X puppy consumed less than 100 g of food in a single day (this occurred only twice in the 1X group and once in the 3X group during this period). Two 5X animals also exhibited abnormal neurological signs, considered treatment-related. These included salivation, ataxia, inability to walk properly, trismus (inability to properly open the mouth), walking in a circle to the right, resting head against the wall, generalized tremors, one episode of seizures (clonic convulsions), "dullness," and regular retropulsion of the neck in one animal and salivation, ataxia, unsteadiness on hind limbs and gait incoordination due to weakness, and slight generalized tremors in the other animal. There were no apparent treatment-related effects on clinical chemistry parameters or serum thyroxin and thyroid stimulating hormone concentrations.

   This companion animal safety study with 8 week old puppies does not demonstrate an adequate margin of safety. In particular, some of the effects observed in 3 of the 5X animals were severe and required veterinary intervention (these 5X puppies received IV saline treatments as well as other treatments and one of these was also treated with oxygen by face mask for 30 minutes on Study Day 4). This study in puppies is classified as **Unacceptable/Guideline.** It **does not satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in juvenile dogs.

4. In the other companion animal safety study with 8 week old puppies (MRID 48487302) one 5X female exhibited profuse salivation on the morning of day 3, exhibited ataxia, generalized tremors, "dullness," and lateral recumbency on days 3-4, and was subsequently euthanized for humane reasons on day 4. There were no gross or microscopic findings to account for the neurological signs; chronic active inflammation with hemorrhage was present in a localized area of one lung, but the study pathologist did not consider these changes extensive enough to cause clinical signs. The 5X males gained less weight than controls during days -1 to 7 (49% less than controls), and 5X animals of both sexes had biologically and statistically significantly decreased mean food consumption on days 1-3 (25-29% less than controls; $p<0.01$).

   It is concluded that toxicity was evident at the 5X dose level as abnormal neurological clinical signs (ataxia, generalized tremors, and profuse salivation) were observed in one female along with decreased food consumption in both sexes on Days 1 through 4 and decreased body weight gain in males. therefore, an adequate margin of safety has not been demonstrated in 8-week-old puppies.

   This companion animal safety study in 8 week old puppies does not demonstrate an adequate margin of safety and is classified as **Unacceptable/Guideline.** It does not satisfy the guideline requirement for a companion animal safety study (OPPTS 870.7200) in juvenile dogs.

5. Refer to the attached DERs for additional comments regarding these studies.

6. The material in MRID 48467119 includes a comparison of dosage rates of other existing permethrin-containing spot-on products and fipronil-containing spot-on products. However, there is no registered spot-on product which contains both of these active ingredients, and it is not known whether there is any additive and/or synergistic toxicity when permethrin and fipronil are combined.

DATA EVALUATION RECORD

PERMETHRIN, FIPRONIL
[104.05 (EFFITIX™ TOPICAL SOLUTION FOR DOGS)]

OPPTS 870.7200
STUDY TYPE: COMPANION ANIMAL SAFETY STUDY- ADULT DOGS
MRID 48467117

Prepared for
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Task Order No. 3-C-03

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Risk Assessment Branch VII, Health Effects Division (7509P) Date: 10/7/2011

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety Study - Adult Dogs; OPPTS 870.7200

PC CODES: 109701, 129121 **DP BARCODE:** 390818

TEST MATERIAL (PURITY): 104.05 (6.71 g/100 mL Fipronil and 50.26 g/100 mL Permethrin; Batch No. CGA 09007-1)

SYNONYMS: Effitix™ Topical Solution for Dogs

CITATIONS: Smith, D. (2010) 104.05:Target animal safety study by dermal administration to beagle dogs. Huntingdon Life Sciences, Cambridgeshire, U.K. Study Number VRB0017, February 5, 2010. MRID 48467117. Unpublished.

Anonymous (2011) Summary of companion animal safety data for Effitix™ Topical Solution for Dogs (Fipronil 6.01% and Permethrin 44.88% end use product). Virbac, 1ère Avenue, 06511 Carros Cedex, France. Study number Virbac 104.05-2, April 10, 2011. MRID 48467119. Unpublished.

Ballantine, A. (2010) Validation of an immunoassay method for the measurement of TSH in canine serum. Huntingdon Life Sciences Ltd., Huntingdon Research Centre, Cambridgeshire, U.K. Study number HLS0715, May 24, 2010. MRID 48467120. Unpublished.

SPONSOR: Virbac S.A., 13eme Rue LID, BP27, Carros, F-06511, France.

EXECUTIVE SUMMARY: In a 14-day companion animal safety study (MRID 48467117), 104.05 (6.71 g/100 mL Fipronil and 50.26 g/100 mL Permethrin; Batch No. CGA 09007-1) was applied topically to the skin on the dorsal midline at the base of the head to the mid back. Groups of six male and six female adult beagle dogs (9-10 months old; Day -1 weights: males: 11.8-14.6 kg; females: 10.1-13.1 kg) were treated at 1X (2.0 mL/dog) or 5X (10.0 mL/dog) the total dosing volumes for the end use product in dogs weighing 10-20 kg. "104.05 Placebo" was applied to a control group of 6 male and 6 female animals at a dosing volume of 10.0 mL/dog. Animals were treated on day 0 and observed for 14 days. Dogs treated with 10.0 mL of the test material or placebo received two separate 5.0 mL applications, spaced at approximately 4 hours apart.

There were no treatment-related effects on mortality, body weight or body weight gain, food consumption, hematology, clinical chemistry, or coagulation parameters, or serum thyroxin and thyroid stimulating hormone concentrations. Treatment at 5X the recommended therapeutic dose resulted in an increased incidence of loose feces within 4 to 8 hours of dosing; three 5X dogs exhibited a total of seven incidences compared to no incidences in controls. In the absence of

correlated effects on body weight or other end points, at this low incidence, the loose feces are not considered adverse. There was no local irritation (erythema/edema) or discoloration of the skin at the dose sites. Cosmetic effects, such as greasy appearance to the hair coat, deposits, spiking, and clumping, were transient and resolved within 7-8 days of dosing.

It is concluded that the margin of safety in 10- to 20-kg adult beagle dogs administered 104.05 [End-use Product: Effitix™ Topical Solution for Dogs] is at least 5x the recommended dose (2.0 mL/dog).

This companion animal safety study in dogs is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in adult dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided for the study report (MRID 48467117). Signed and dated GLP and Data Confidentiality statements were provided for the companion animal safety summary (MRID 48467119); the GLP Compliance Statement consisted of a declaration that, as a compilation document, the volume "is not subject to the requirements of 40 CFR Part 160."

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: 104.05 [End-use Product: Effitix™ Topical Solution for Dogs]

Description:	Clear, slightly yellow solution
Batch #:	CGA 09007-1
Purity:	6.71 g/100 mL Fipronil and 50.26 g/100 mL Permethrin
Compound Stability:	Re-test date: September 2009; stored in original packaging, at ambient temperature (≤ 25° C), dry conditions.
CAS #:	Not Provided

2. Vehicle control: 104.05 Placebo

Description:	Liquid
Batch #:	NDE 10132
Purity:	0.02% (w/v) Butylhydroxyanisole, 0.01% (w/v) Butylhydroxytoluene, and Ethylene diethylene glycol (QSP 100 mL)
Compound Stability:	Re-test date: September 2009; stored in original packaging, at ambient temperature (≤ 25° C), dry conditions.
CAS #:	Not Provided

3. **Test animals:**

Species:	Dog	
Breed:	Beagle	
Age/weight at study initiation:	Approximately 9-10 months old/ Males: 11.8-14.6 kg; Females: 10.1-13.1 kg	
Source:	Harlan Laboratories UK Ltd.	
Housing:	Individually, in partitioned kennels with underfloor heating (dimensions not provided)	
Diet:	400-450 g of Teklad 2021 Dog Maintenance Diet, moistened with an equal amount of water. Dogs were allowed access to the food for at least one hour.	
Water:	*Ad libitum* water from the public supply	
Environmental conditions:	**Temperature:**	15-24° C.
	Humidity:	Generally 40-70%, with occasional excursions to (35-92%)
	Air changes:	Approximately 12/hour
	Photoperiod:	12 hours light/12 hours dark
Acclimation period:	Four weeks.	

B. STUDY DESIGN:

1. **In life dates:** Start: July 2, 2009; End: July 16, 2009.

2. **Animal assignment:** Study design is given in Table 1. The animals were assigned to groups according to body weight on day -23, using a stratified pseudo-random procedure, such that inclusion of litter-mates within the same group was avoided to the extent possible and the group mean body weights for each sex were approximately equal.

TABLE 1: Study design [a]

Test Group	Dosing volume (mL/dog)	Dose (mg/dog)		Dose (mg/kg) [b]		Number assigned	
		Fipronil	Permethrin	Fipronil	Permethrin	Males	Females
1. Control	10.0 mL (2 applications of 5.0 mL of control item)	0	0	0	0	6	6
2. 1X	2.0 mL (1 application of 2.0 mL of test item)	134	1000	9.2-12.9	69.0-96.2	6	6
3. 5X	10.0 mL (2 applications of 5.0 mL of test item)	670	5000	46.2-64.4	342.5-495.0	6	6

[a] Data taken from pp. 14, 18, and 106-107 MRID 48467117.

[b] Calculated by reviewer, using day -1 body weight ranges of 10.4-14.5 kg and 10.1-14.6 kg for the 1X and 5X groups, respectively.

3. **Dose selection rationale:** According to the study report, a 2-mL dosing volume is the intended recommended therapeutic dose for this product for dogs that weigh 10-20 kg. Doses were selected to comply with OPPTS 870.7200. The exaggerated doses were achieved via two 5.0 mL applications (spaced approximately 4 hours apart) of the end-use product or the control item. [redacted]

4. **Treatment:** The control or test material, as appropriate, was applied topically on day 0, using a syringe without a needle. The application site was from the dorsal cervical area at the base of the head to the mid back. To achieve the exaggerated 5x doses, the control or test material was

applied on two occasions with 4 hours between applications. There was no mention of parting the hair or making a particular effort to apply the materials directly to the skin.

5. Statistics:

Body weight gain (days -1 to 7, days 7 to 14, and days -1 to 14), mean food consumption (over days 0-14), and hematology and clinical chemistry parameters were analyzed as follows. For clinical pathology data, if greater than 75% of the values were identical, Fisher's exact test was used. Otherwise, the data were first analyzed using Bartlett's test for homogeneity of variances. Data with homogenous variances were analyzed using the F_1 approximate test, followed by Dunnett's test (if significant) or Williams' test (if not significant). If the variances were non-homogenous, logarithmic and square root transformations were done, and the transformed data were analyzed as above if the variances were stabilized; if not, the untransformed data were analyzed using the non-parametric H_1 test, followed by Steel's test (if significant) or Shirley's test (if not significant). The individual animal was considered the basic experimental unit, and the data for each sex were analyzed separately. Differences from the control were considered significant at the 5.0% and 1.0% probability levels.

The reviewer, in general, considers the above-mentioned analyses to be appropriate; however, it would have been preferable for investigators to analyze the absolute body weight and daily food consumption data in addition to the body weight gains and cumulative food consumption.

C. METHODS:

1. Observations:

a. General health observations: During acclimation, the animals were observed at least once per day. From at least day -14 through the end of the study, the animals were visually inspected at least twice daily for abnormal clinical signs, including the presence of vomitus, blood, diarrhea, etc., in the pens. On day 0, detailed observations were made 11-33 minutes prior to each dose application, during and immediately after each dose application, and approximately hourly after the first dose application until 8 hours after the second dose application (for the control and 5X groups) or approximately hourly for 4 hours and at 7 and 12 hours after dosing (for the 1X group). The post-dosing detailed observations included observation for any behavioral indications of irritation or other reaction to treatment, such as pawing or scratching at the application site. These included evaluation of the animals while the animals were standing or walking around in order to discern any ataxia, loss of coordination, or localized or generalized tremors.

b. Clinical assessments: All animals received detailed physical examinations on days -3, 1, 7, and 14. The examination included assessment of general appearance, color of mucous membranes, behavior, appetite, stool characteristics, eyes, ears, and the respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological, and integumentary systems. Respiratory rate, heart rate, and temperature were recorded.

c. Application site observations: After treatment, the application site was observed daily for changes to the skin and fur. Any erythema/eschar and edema were scored according to the Draize scale, and the presence or absence of changes to the hair, such as matting (tangled mass of hair), greasy appearance, clumping (areas of compact clusters or lumps), spiking (hair coming together

in narrow, sharp points), discoloration, and deposits (areas of test item visible on the surface), were also recorded.

2. **Body weight:** The animals were weighed twice weekly during acclimation (except once weekly during week -3) and on days -1, 7, and 14.

3. **Food consumption:** Food consumption was measured and recorded daily.

4. **Clinical pathology:** On day -8, day 1 (approximately 22-24 hours after the first application), and day 7, blood for hematology, clinical chemistry, coagulation evaluation, and thyroid function evaluation was collected from the jugular vein or another suitable vein. On sampling days, food was not offered to the animals until after blood sampling was performed. The CHECKED (X) parameters were examined.

a. **Hematology:**

X	Hematocrit (HCT)*	X	Leukocyte differential count* (absolute and percentage)
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count	X	Reticulocyte count
	Blood clotting measurements	X	Morphology (if indicated)
X	(Thromboplastin time)*	X	Heinz body formation
	(Clotting time)		
X	(Prothrombin time)*		

* Recommended for companion animals safety evaluation based on OPPTS 870.7200

b. **Clinical chemistry:**

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Urea nitrogen (BUN)*
X	Phosphorus*		Cholesterol
X	Potassium*	X	Globulins*
X	Sodium*	X	Glucose*
	ENZYMES	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Direct bilirubin*
	Cholinesterase (ChE)		Indirect bilirubin
	Creatine phosphokinase	X	Total protein (TP)*
	Lactic acid dehydrogenase (LDH)		Triglycerides
X	Alanine aminotransferase (ALT/also SGPT)*		Serum protein electrophoresis
X	Aspartate aminotransferase (AST/also SGOT)*		Albumin/globulin ratio
	Sorbitol dehydrogenase		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Recommended for a companion animal safety evaluation based on OPPTS 870.7200.

e. **Thyroid function:** Serum thyroxin (T4) and thyroid stimulating hormone (TSH) immunoassays were done. The separated serum was stored at approximately -20° C until analysis. Where

possible, the test samples were run in duplicate, and the calculated mean T4 and TSH concentrations were reported. For both parameters, any test results with duplicate results greater than ±20% from their mean result were reanalyzed, provided there was a sufficient volume of serum remaining; if reanalysis could not be accomplished due to insufficient sample remaining, then the initial mean result was reported "for information only." Due to sample volume limitations, some samples could only be analyzed for TSH as single measurements, and, in some of these instances, TSH analyses were run using a 1 in 2 dilution. The results from diluted samples were also reported "for information only."

5. **Urinalysis:** Urinalysis is not required for companion animal safety studies and was not done as part of the current study.

6. **Sacrifice and pathology:** There were no deaths or moribund sacrifices during the study. Terminal sacrifices and gross necropsies were not done and are not required under OPPTS 870.7200.

II. RESULTS

A. ACTUAL DOSES ADMINISTERED: The mg/kg doses of the active ingredients are given in Table 1.

B. OBSERVATIONS:

1. **Clinical signs of toxicity:** Selected clinical signs data are given in Table 2. The incidences of loose feces from 5X animals between 4 and 8 hours after the second dose are considered potentially treatment-related, although the observed incidences are fairly low. One 5X female (#362) had five occurrences of loose feces in the post-dosing period (4, 5, 6, 7 and 8 hours after the second dose). The incidences of vomiting from 1X and 5X animals later in the course of the study (between days 4 and 13) are not considered treatment-related.

   The most common observation from the physical exams was nervous behavior, which was noted in 1-5 animals per group, including controls, without evidence of a dose response pattern. Other observations mainly included cutaneous lesions, scabs, dermatitis, scars, scale on the teeth, and other observations that are common in laboratory beagles.

TABLE 2: Vomiting and loose feces from adult beagles treated with 104.5 or 104.05 Placebo [a]			
Observation	Dosage		
	Control	1X	5X
Loose feces [b]:			
Day 0, post-dosing	0	0	3 dogs[b] [7 incidences]
Days 1-14	1 dog [2 incidences]	4 dogs [5 incidences]	2 dogs [3 incidences]
Total	1 dog [2 incidences]	4 dogs [5 incidences]	4 dogs [10 incidences]
Vomiting:			
Day 0, post-dosing	0	0	0
Days 1-14	0	2 dogs [3 incidences]	3 dogs [3 incidences]
Total	0	2 dogs [3 incidences]	3 dogs [3 incidences]

[a] Data compiled from Appendix 5, pp. 100-102, MRID 48467117.

[b] One female (#362) had five occurrences of loose feces in the post-dosing period (4, 5, 6, 7 and 8 hours after second dose).

2. **Quantitative physical signs parameters:** There were no treatment-related effects on respiratory rate, pulse rate, or body temperature. Mean values of the treated males and females were generally similar to those of their respective controls, and the differences that were seen were present prior to treatment or did not follow a dose response pattern.

3. **Local effects at the application site:** Prior to the application of the second dose to one 5X female (#366), it was noted that the material from the first application had spread towards the lower back and extending down to the lower right hind leg.

   There were no observations of erythema, edema, or matting. On day 0, all of the animals had a greasy appearance to the hair coat, and most also had deposits, while four controls, seven 1X animals, and nine 5X animals had spiking. Cosmetic effects with onset on day 1 included clumping on two controls and six 5X animals and the appearance of spiking on an additional 5X animal. Controls were free of cosmetic effects by day 3, and the 3x and 5X animals were free of cosmetic effects by days 7-8.

3. **Mortality:** There were no deaths or moribund sacrifices.

C. **BODY WEIGHT AND WEIGHT GAIN:** Body weight data are given in Table 3. There were no treatment-related effects on body weight or body weight gain.

TABLE 3: Body weight and food consumption data from adult beagles treated with 104.5 or 104.05 Placebo [a]				
Parameter/ Study day or interval		Dosage		
		Control	1X	5X
Males				
Body weight (kg):	Day -7	13.5±0.68	13.5±0.78	13.5±1.03
	Day -1	13.4±0.62	13.4±0.93	13.7±0.75
	Day 7	13.5±0.62	13.6±0.86	13.7±0.75
	Day 14	13.5±0.70	13.6±0.92	13.9±0.67
BW change (kg):	Days -7 to -1 [b]	-0.1	-0.1	0.2
	Days -1 to 7	0.03±0.163	0.18±0.172	0.03±0.103
	Days 7 to 14	0.05±0.187	-0.03±0.151	0.18±0.098
	Day -1 to 14	0.08±0.248	0.15±0.084	0.22±0.147
Mean overall food consumption (days 0-14) in g/animal/day		448±2.7	424±41.2	435±37.0
Females				
Body Weight (kg):	Day -7	10.9±1.16	10.8±0.57	10.5±0.90
	Day -1	11.1±1.10	10.9±0.49	10.9±0.75
	Day 7	11.2±1.14	11.0±0.42	11.0±0.74
	Day 14	11.4±1.21	11.1±0.50	11.2±0.76
BW change (kg):	Days -7 to -1 [b]	0.2	0.1	0.4
	Days -1 to 7	0.05±0.055	0.15±0.207	0.12±0.160
	Days 7 to 14	0.20±0.200	0.07±0.121	0.23±0.151
	Day -1 to 14	0.25±0.217	0.22±0.214	0.35±0.152
Mean overall food consumption (days 0-14) in g/animal/day		408±39.1	417±36.8	419±26.8

[a] Data taken from Tables 2 and 3, pp. 43-44 and 45-50, respectively, MRID 48467117. Values are Mean ± Standard Deviation, with n=6 for all groups.

[b] Calculated by reviewer using group mean absolute body weight values.

D. **FOOD CONSUMPTION:** Mean overall food consumption over the study interval (days 0-14) is given in Table 3. The mean overall food consumption and daily food consumption values of the treated males and females were similar to their respective controls.

E. **BLOOD ANALYSES:**

1. **Hematology and coagulation parameters:** Statistically significant differences were found for some hematology parameters at one or more time points, including decreased mean monocyte counts in 5X males on days 1 and 7 and increased mean neutrophil counts in 5X females on day 7. However, none of the statistical findings were considered biologically significant or treatment-related because the differences were small in magnitude, with the mean values falling within two standard deviations of the control mean and within the background ranges of the testing laboratory (data not provided in the study report). The coagulation parameter values of the treated males and females were similar to those of their respective controls.

2. **Clinical chemistry:** Statistically significant differences were found for some parameters, but all differences were present without a dose-related trend or were of small magnitude with the mean

values falling within two standard deviations of the control mean and/or within the background ranges of the testing laboratory (data not provided in the study report); thus none were considered biologically significant.

3. **Thyroid function evaluation:** The results of the thyroxin (T4) and thyroid stimulating hormone (TSH) assays are given in Table 4. Six individual TSH results (from five females and one male) were reported "for information only" because they were analyzed as a single measurement following dilution or because there was insufficient sample volume to repeat an analysis when the results from the duplicate samples were greater than 20% from their mean. However, these "for information only" results were included in calculation of group mean values. No clear treatment-related effects were evident; however, it must be noted that, for both parameters, the data were quite variable, with most of the coefficients of variation for T4 >21% and all of the available coefficients of variation for TSH ≥ 66%. Some of the individual results appeared abnormal: one control male had low T4 concentration on days 1 and 7 (9.41 and 9.25 nmol/L, respectively), without any concomitant alteration in TSH; one control male had elevated TSH concentration at all time points (0.600-0.699 ng/mL), without any concomitant alteration in T4; and T4 was greater than 37 nmol/L in several animals from the control and 5X groups (three control males and one control female on day 1, one 5X male on days -8, 1, and 7, one 5X male and two 5X females on day 1, only, and one 5X female on day 7, only).

TABLE 4: Mean thyroxin (T4) and thyroid stimulating hormone (TSH) concentrations in adult beagles treated with 104.5 or 104.05 Placebo [a]

Parameter / Study day	Dosage		
	Control	1X	5X
Males			
T4 (nmol/L): Day -8	32.6±7.0	22.8±5.6	29.0±10.0
Day 1	35.0±7.8	21.3±7.7	31.8±10.1
Day 7	27.5±4.1	17.8±5.2	31.2±10.0
TSH (ng/mL): Day -8	0.250±0.259	0.200±0.132	0.182±0.139
Day 1 [n=6, 4, and 6]	0.222±0.228	BLQ [b] (<0.140)	BLQ (<0.140)
Day 7	0.181±0.271	BLQ (<0.140) [c]	BLQ (<0.140)
Females			
T4 (nmol/L): Day -8	23.4±9.1	23.7±6.3	24.9±7.7
Day 1	27.6±8.3	23.4±5.7	29.4±12.1
Day 7	26.7±8.1	25.0±4.3	28.5±6.5
TSH (ng/mL): Day -8	BLQ (<0.140)	0.145±0.125	BLQ (<0.140)
Day 1	0.140±0.118 [c]	BLQ (<0.140) [c]	BLQ (<0.140)
Day 7	BLQ (<0.140)	BLQ (<0.140) [d]	BLQ (<0.140) [c]

[a] Data taken from pp. 158 and 162, MRID 48467117. Values are Mean ± Standard Deviation, with n=6 for all groups, except as indicated.

[b] BLQ = below the limit of quantification.

[c] Mean includes one value that was reported "for information only."

[d] Mean includes two values that were reported "for information only."

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that topical application of the test substance, 104.05, at 5X the intended dosing volume resulted in an increased incidence of loose feces on the day of dosing, but that this dose level was otherwise well tolerated.

B. **REVIEWER COMMENTS:** The reviewer is in agreement with the study author. While treatment-related, in the absence of correlated effects on any of the other evaluated endpoints, the increased incidence of loose feces within 4-8 hours of dosing is not considered adverse.

It is concluded that the margin of safety in 10- to 20-kg adult beagle dogs administered 104.05 [End-use Product: Effitix™ Topical Solution for Dogs] is at least 5x the recommended dose (2.0 mL/dog).

C. **STUDY DEFICIENCIES:** No major deficiencies were identified.

DATA EVALUATION RECORD

PERMETHRIN; FIPRONIL
[EFFITIX™ TOPICAL SOLUTION FOR DOGS / 104.05]

STUDY TYPE: COMPANION ANIMAL SAFETY STUDY- PUPPIES; OPPTS 870.7200
MRID 48467118

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Task Order No. 3-C-03

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Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety Study - Puppies; OPPTS 870.7200

PC CODES: 109701, 129121 **DP BARCODE:** 390818

TEST MATERIAL (PURITY): 104.05 (6.62 g/100 mL Fipronil and 50.3 g/100 mL Permethrin; Batch #NDE 10189)

SYNONYMS: Effitix™ Topical Solution for Dogs

CITATIONS: Gupta, S. (2011) A 14-day tolerance study in beagle pups when administered 104.05 (6.7% Fipronil and 50% Permethrin topical solution) topically at 1X, 3X and 5X the recommended dose. Charles River Laboratories Preclinical Services Ireland Ltd., Carrentrila, Ballina, Co. Mayo, Ireland. Study Number F004\10-003, April 6, 2011. MRID 48467118. Unpublished.

SPONSOR: Virbac S.A., Pre-clinical and Clinical Unit (VB7), 13eme Rue Lid - B.P. 27, 06511 Carros Cedex, France.

EXECUTIVE SUMMARY: In a 14-day companion animal safety study (MRID 48467118), 104.05 [6.71 g/100 mL Fipronil and 50.26 g/100 mL Permethrin; Batch No. CGA 09007-1 (T3MOIS 5° C)] was applied topically to the skin on the dorsal midline from the base of the head to the rump area (this is inconsistent with the proposed label which states the entire applicator contents should be squeezed onto the dog's skin at a single site for small dogs and puppies 8 weeks or older weighing up to 22.9 lbs). Groups of six male and six female 50-57 day old (approximately 8-week-old, weighing from 1.5 to 3.4 kg) beagle puppies were treated at 1X (1.0 mL/puppy), 3X (3.0 mL/puppy), or 5X (5.0 mL/puppy) the total recommended dosing volume for the end use product in puppies weighing less 10 pounds. "104.05 Placebo" was applied in identical manner to a control group of 6 male and 6 female animals at a dosing volume of 5.0 mL/puppy. The 1X and 3X puppies were treated once; the 5X and placebo puppies received two divided doses of 2.5 mL approximately 4 hours apart. Animals were treated on day 0 and observed for 14 days.

Effects were seen that were dose-related. At the 5X dose level there were increased incidences of vomiting and abnormal feces, i.e. feces that were liquid, loose, mucoid, with traces of blood, and/or discolored (seen in 4-5 5X animals vs. 0 controls). The 5X animals of both sexes had decreased weight gain during days -1 to 7 (51% and 55% less than controls for males and females, respectively). During days 1-5 of the study, the daily food consumption of the 5X animals was 32-50% less than that of controls ($p<0.01$), and there were 26 occasions (involving nine 5X puppies) in the period from Day 1 to 9 when a 5X puppy consumed less than 100 g of food in a single day (this occurred only twice in

the 1X group and once in the 3X group during this period). Two 5X animals also exhibited abnormal neurological signs, considered treatment-related. These included salivation, ataxia, inability to walk properly, trismus (inability to properly open the mouth), walking in a circle to the right, resting head against the wall, generalized tremors, one episode of seizures (clonic convulsions), "dullness," and regular retropulsion of the neck in one animal and salivation, ataxia, unsteadiness on hind limbs and gait incoordination due to weakness, and slight generalized tremors in the other animal. There were no apparent treatment-related effects on clinical chemistry parameters or serum thyroxin and thyroid stimulating hormone concentrations.

In this study, one animal tested positive for coccidia while abnormal feces consistent with coccidia (i.e. mucoid or loose with mucus and/or frank blood) were seen in what appeared to be a dose-related manner. One animal that died during the week prior to treatment had pneumonia. Baseline blood work revealed that 1-2 animals per group had normocytic normochromic or microcytic hypochromic anemia on day -7, and one animal had leukopenia. Elevated WBC and neutrophils on day 7 in two 5X animals (#36094 and #87310) suggest the possibility that their serious abnormal clinical signs may have been at least partly due to infection. As a result, alterations in the hematology parameters are uninterpretable because of the possible compromised health status of the animals as an additional contributing factor.

This companion animal safety study in 8 week old puppies does not demonstrate an adequate margin of safety. In particular, some of the effects observed in 3 of the 5X animals were severe and required veterinary intervention (these 5X puppies received IV saline treatments as well as other treatments and one of these was also treated with oxygen by face mask for 30 minutes on Study Day 4). This study in puppies is classified as **Unacceptable/Guideline.** It **does not satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in juvenile dogs. It should be noted that an earlier limit test in 8 week old puppies (MRID 48487302) preceded this full study, and one 5X female was sacrificed (for humane reasons) on Day 4 after showing neurological symptoms.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided for the study report (MRID 48467118). Signed and dated GLP and Data Confidentiality statements were provided for the companion animal safety summary (MRID 48467119); the GLP Compliance Statement consisted of a declaration that, as a compilation document, the volume "is not subject to the requirements of 40 CFR Part 160."

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: 104.05 [End-use Product: Effitix™ Topical Solution for Dogs]

Description:	Liquid
Batch #:	NDE 10189
Purity:	6.62 g/100 mL Fipronil and 50.3 g/100 mL Permethrin
Compound Stability:	Expiration date: July 2011; stable under the storage conditions used in the study (in original packaging, at 18-22° C.)
CAS #:	Not Provided

2. Vehicle control: 104.05 Placebo

Description:	Liquid
Batch #:	NDE 10190
Purity:	0.02% (w/v) Butylhydroxyanisole, 0.01% (w/v) Butylhydroxytoluene, and Ethylene diethylene glycol (QSP 100 mL)
Compound Stability:	Expiration date: July 2011; stable under the storage conditions used in the study (in original packaging, at 18-22° C.)
CAS #:	Not Provided

3. Positive control: No positive control was used.

4. Test animals:

Species:	Dog	
Breed:	Beagle	
Age/weight at study initiation:	50-57 days old/ Males: 1.5-3.4 kg (on day -1); Females: 1.5-2.7 kg (on day -1)	
Source:	Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Co. Mayo, Ireland	
Housing:	Prior to weaning (day -7): puppies were housed with dams in two adjoining pens (each 1.7 m x 1.4 m) with the dividing gate opened, except during daily 2- to 3-hour intervals, during which the dam was separated from the puppies to prepare them for weaning; Days -7 through -3: puppies were housed in groups of two or three; Days -2 through 14: puppies were housed individually in pens measuring 1.7 m x 1.4 m. Infrared lamps were provided when deemed necessary.	
Diet:	Pedigree pup food (Pedigree Masterfoods, Melton Mowbray, Leicester, U.K.), approximately 400 g/pup/day Supplemental food (e.g. Welpi® milk replacer) was offered to pups when deemed necessary.	
Water:	*Ad libitum* potable water via automatic drinkers or stainless steel bowls	
Environmental conditions:	**Temperature:**	16-19° C.
	Humidity:	40-79%
	Air changes:	Not reported
	Photoperiod:	Not reported
Acclimation period:	Fourteen days.	

B. STUDY DESIGN:

1. In life dates: Start: September 7, 2010; End: November 16, 2010.

2. **Animal assignment:** Study design is given in Table 1. The study was conducted in five replicates, as pups of the appropriate age became available. Between days -3 and 0, the animals from each replicate were assigned to groups according to body weight, using a stratified randomized block design. All pups meeting the inclusion criteria were ranked within sex in order of decreasing body weight, with any same-sex pups of identical body weight ranked in order of decreasing microchip number. To the extent possible, blocks of four same-sex pups were formed and then randomly allocated to study groups using random order numbers derived from Fisher and Yates tables. When necessary, an incomplete block would be completed using pups from the subsequent set. Table 2 lists the number of pups in each set that were assigned to each group. The study was not blinded.

TABLE 1: Study design [a]

Test Group	Dosing volume (mL/puppy)	Dose (mg/puppy)		Dose (mg/kg) [b]		Number assigned	
		Fipronil	Permethrin	Fipronil	Permethrin	Males	Females
1. Control	5 mL (2 applications of 2.5 mL of vehicle control)	0	0	0	0	6	6
2. 1X	1 mL (1 application of 1.0 mL of test item)	66.2	503	24.5-44.1	186.3-335.3	6	6
3. 3X	3 mL (1 application of 3.0 mL of test item)	198.6	1509	70.9-104.5	538.9-794.2	6	6
4. 5X	5 mL (2 applications of 2.5 mL of test item)	331.0	2515	97.4-183.9	739.7-1397	6	6

[a] Data taken from pp. 24 and 50, MRID 48467118.

[b] Calculated by reviewer, using day -1 body weight ranges of 1.5-2.7 kg, 1.9-2.8 kg, and 1.8-3.4 kg for the 1X, 3X, and 5X groups, respectively.

TABLE 2: Study design [a]

Test Group	Sets				
	1	2	3	4	5
1. Control	1 M, 1 F	2 M, 2 F	1 F	2 M, 2 F	1 M
2. 1X	1 M, 2 F	2 M, 2 F	--	2 M, 2 F	1 M
3. 3X	1 M, 1 F	1 M, 2 F	1 M, 2 F	2 M, 1 F	1 M
4. 5X	1 M, 2 F	1 M, 2 F	1 M, 1 F	1 M, 1 F	2 M

[a] Data compiled by reviewer using Table 1, p. 49, MRID 48467118.
M = male; F = female.

3. **Dose selection rationale:** According to the study report, a 1-mL dosing volume is the normal recommended dose for this product for dogs, and presumably for puppies, weighing less than 10 kg. The doses used in the study were selected to conform with OPPTS 870.7200, i.e. 1X, 3X, and 5X the recommended dose, and the 5X dose was achieved with two 2.5 mL applications of the end-use product, with the applications approximately 4 hours apart. The vehicle control substance was also administered at 5 times the normal recommended dosing volume of the product (two 2.5 mL applications which were approximately 4 hours apart). [redacted]

[redacted]. It should be noted that an earlier limit test in puppies (MRID 48487302) preceded this full study.

4. **Treatment:** The control or test material, as appropriate, was applied topically on day 0, using a syringe without a needle. For each application, the tip of the syringe was positioned on the dorsal cervical area at the base of the pup's head and used to separate the pup's hair so the material could be applied at the skin level, and the contents of the syringe were then applied, as evenly as possible, from the base of the head to the rump area. Following application, the pup was restrained in an upright position for at least two minutes to prevent run-off of the test or control substance. Syringe volumes were visually confirmed immediately prior to administration, and each syringe was checked after administration to ensure that none of the contents remained. To achieve the exaggerated 5x doses, the control or test material was applied on two occasions with 4 hours (± 10 minutes) between the two applications. There was no evidence of run-off

5. **Statistics:**

Descriptive statistics were generated for all endpoints (separately by sex and combined) at each time point.

Body weight and food consumption, hematology and clinical chemistry parameters, thyroxin and thyroid stimulating hormone values, were analyzed using repeated measures analysis of covariance (RMANCOVA) including treatment, sampling day, sex, and the interaction terms "treatment by sampling day (group*day)," "treatment by sex" (group*sex), "sex by sampling day" (sex*day), and "treatment by sex by sampling day" (group*sex*day) as fixed effects. The set (replicate) was also included in the model as a fixed factor but was only retained if significant ($p<0.05$). The individual animal was identified as the subject in the repeated statement. The covariate was the pretreatment baseline measurement or the average of the three pretreatment baseline measurements in the case of body weight.

For each analysis, the appropriate variance-covariance matrix structure was selected from among compound symmetry, heterogeneous compound symmetry, first-order autoregressive, and heterogeneous first-order autoregressive, based on the Akaike Information Criterion.

If the group*sex*day interaction was significant ($p<0.05$), then the statistical analysis was considered inconclusive. If the group*sex*day interaction was not significant, the interactions of group*sex and group*day were evaluated. If group*sex was significant at $p<0.05$ but group*day was not significant ($p>0.10$), then the statistical analysis was considered inconclusive. If group*day was significant at $p<0.10$, pair-wise comparisons of each treated group least squares mean was performed against the control group least squares mean at each sampling day, using a two-sided Student's t-test.

When the group*sex, group*day, and group*sex*day interactions were not significant, the "treatment" main effect was evaluated at $p<0.10$. If significant, pair-wise comparisons of each treated group least squares mean was performed against the control group least squares mean, using a two-sided Student's t-test. If not significant, no further analyses were conducted on the variable.

Profile plots were provided for all continuous variables and included baselines (or arithmetic means of pre-study data) and all data collected from day 1 through the end of the study. For each endpoint, the individual data were presented separately for each treatment group (with the sexes combined), and group mean values (for the sexes combined) were presented together, on a single plot.

Potential outliers were verified with the study director, and no outliers were excluded. The following defaults were used for the analyses: hemoglobin values recorded as "<6" were defaulted to 6; creatinine values recorded as "<18" were defaulted to 18; total and direct bilirubin values recorded as "<1.7" were defaulted to 1.7; thyroid stimulating hormone values recorded as "<0.14" were defaulted to 0.14; and thyroxin values recorded as "<6.1" were defaulted to 6.1.

The clinical signs data were not subjected to statistical analysis. No animals died or were sacrificed during the study; therefore, planned statistical analysis of death or sacrifice via logistic regression was not necessary.

C. METHODS:

1. Observations:

a. **General health observations:** Beginning on day -14 and continuing through day -1, general health observations were recorded once daily. No further details were provided concerning the evaluated parameters or whether the evaluations were cage-side or hands-on.

b. **Clinical assessments:** All pups were examined by a veterinarian on days -14 and -1, and pups belonging to sets 3 and 4 were given an additional examination on day -6 or day -12, respectively. On day 0, a veterinarian conducted clinical assessments on all animals prior to the first treatment and at 1 hour (±5 minutes), 2, 3, 4, and 5 hours (±10 minutes), and 6, 7, and 8 hours (±30 minutes) after the final treatment. For the control and 5X animals, clinical assessments were also performed at 1 hour (±5 minutes), and 2, 3, and 4 hours (±10 minutes) after the first treatment. During the remainder of the study interval (days 1-14), clinical assessments were performed by a veterinarian twice daily, once in the morning and once in the afternoon, with at least four hours between assessments. Clinical assessments consisted of observing each animal for at least one minute and recording the presence or absence of the following: lethargy, ataxia, recumbency, paralysis, coma, pruritis, hyperactivity, tremors, convulsions, abnormal mydriasis, abnormal miosis, corneal opacity, dyspnea, tachypnea, coughing, abnormal salivation, vomiting, abnormal mucous membranes, ocular discharge, nasal discharge, cardiovascular changes, abnormal feces, abnormal urine, abnormal coat condition, and abnormalities of the application site. For any finding that was present, a brief comment further describing the condition was made at the first point of detection.

2. **Body weight:** The animals were weighed on days -14, -7, -1, 7, and 14.

3. **Food consumption:** From day -2 through day 13, each puppy was offered a pre-weighed, approximately 400-g quantity of food, and, on the following day, unconsumed food was removed from the pen and weighed.

4. **Clinical Pathology:** Each animal had blood collected for hematology, clinical chemistry, and thyroid function evaluation on day -7, day 1 (24 hours ± 2 hours after the first application), and day 7. Blood was collected for thyroid function evaluation on day 14, and if an animal had any hematology or clinical chemistry parameters outside the reference range on study day 7, an additional sample was collected from that animal on day 14 for re-evaluation of the particular parameter(s). On days -7, 1, 7, and 14, food was not offered to the animals until after blood sampling was performed, but there was no mention of withholding food and/or water for a specific duration of time prior to collection, and the venipuncture site also was not reported. The CHECKED (X) parameters were examined. Coagulation was not evaluated as part of the current study, but these data are available in a previously conducted companion animal safety study in puppies (MRID 48487302).

a. **Hematology:**

X	Hematocrit (HCT)*	X	Leukocyte differential count* (absolute)
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		Morphology (if indicated)
	(Thromboplastin time)*	X	Heinz body formation
	(Clotting time)		
	(Prothrombin time)*		

* Recommended for companion animals safety evaluation based on OPPTS 870.7200

b. **Clinical Chemistry:**

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Urea nitrogen (BUN)*
X	Phosphorus*		Cholesterol
X	Potassium*	X	Globulins*
X	Sodium*	X	Glucose*
	ENZYMES	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Direct bilirubin*
	Cholinesterase (ChE)		Indirect bilirubin
	Creatine phosphokinase	X	Total protein (TP)*
	Lactic acid dehydrogenase (LDH)		Triglycerides
X	Alanine aminotransferase (ALT/also SGPT)*		Serum protein electrophoresis
X	Aspartate aminotransferase (AST/also SGOT)*		Albumin/globulin ratio
	Sorbitol dehydrogenase		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Recommended for a companion animal safety evaluation based on OPPTS 870.7200.

c. **Thyroid Function:** Serum thyroxin and thyroid stimulating hormone assays were done using canine-specific radioactive immunoassays (Siemens), with the results counted using a gamma counter. The separated serum was stored at between -15° C and -30° C until shipment on dry ice

to the analyzing laboratory (Charles River Laboratories, Central Laboratory Services, Edinburgh, U.K.).

5. **Urinalysis:** Urinalysis is not required for companion animal safety studies and was not done as part of the current study.

6. **Sacrifice and Pathology:** There were no deaths or moribund sacrifices during the study. Terminal sacrifices and gross necropsies were not done and are not required under OPPTS 870.7200.

II. RESULTS

A. **ACTUAL DOSES ADMINISTERED:** The mg/kg doses of the active ingredients are given in Table 1.

B. **OBSERVATIONS:**

1. **Clinical signs of toxicity:** Selected clinical signs data are given in Table 3. There were treatment-related increased incidences of vomiting and abnormal stools in 5X puppies, with a total of seven 5X puppies affected. One of the puppies (#36094) that exhibited both vomiting and diarrhea became dehydrated and had slightly pale mucous membranes. A fecal from this puppy was positive for coccidia, but, while other treatments were given [intravenous normal saline and amoxicillin/potassium clavulanate (3 days)] the animal was not treated for coccidia.

   Two puppies exhibited neurological signs. The first of these (#40074) had onset of signs on day 2 and exhibited such neurological signs as salivation, ataxia, inability to walk properly, trismus, walking in a circle to the right, resting its head against the wall, generalized tremors, one episode of seizures (clonic convulsions), "dullness," and regular retropulsion of the neck, along with respiratory signs (dyspnea, increased respiratory sounds, rate, and intensity, green nasal discharge, froth from the mouth, and fluid sounds in the lungs and nose), vomit, slightly loose feces with traces of fresh blood, and lethargy. This puppy was treated with Buscopan compositum®, intravenous normal saline, Rimadyl injection, amoxicillin/potassium clavulanate (5 days), glucose (5%w/v, i.v.), oxygen via mask administration, and intramuscular dexamethasone (given on day 3) and recovered by day 7. The second of these (#87310) had decreased appetite and had a thin appearance beginning on day 5, followed by moderate salivation, ataxia, unsteadiness on hind limbs and gait incoordination due to weakness, slight generalized tremors, preference for ventral recumbency when made to stand up, slightly pale mucous membranes with normal capillary refill time, and vomiting. This puppy was treated with intravenous normal saline, Rimadyl injection, amoxicillin/potassium clavulanate (5 days), glucose (5% w/v, i.v.), and intramuscular dexamethasone (given on day 8) and recovered by day 10.

   An additional 5X puppy (#34880) was observed to be "dull" on day 3, without any other abnormal clinical signs noted at any time point during the study.

TABLE 3: Vomiting and abnormal feces from puppies treated with 104.5 or 104.05 Placebo [a]				
Observation	Dosage			
	Control	1X	3X	5X
Abnormal feces [b]:				
Incidence	0	1	1	15
# Affected pups	0	1	1	5
First / last days noted	Not applicable	Day 5	Day 0 (before 1st treatment)	Day 0 (before 2nd treatment) / Day 6
Vomiting:				
Incidence	0	0	0	7
# Affected	0	0	0	4
Days noted	Not applicable	Not applicable	Not applicable	Day 0 (before 2nd treatment) / day 2

[a] Data compiled from Table 4, p. 52, MRID 48467118.

[b] Includes feces that were liquid, loose, mucoid, with traces of blood, and/or discolored (green or yellow).

2. Cosmetic effects: On day 0, clumping and a greasy appearance of the hair coat were observed on all animals beginning within one hour of the first application, and other changes such as matting, spiking, and deposits were noted on 1-3 animals in the control, 3X, and 5X groups, with a later onset, 3-5 hours after the initial treatment. On day 1, additional deposits were noted on 1-2 animals from each of the control, 1X, and 3X groups, although the cosmetic effects had already fully resolved in some of the animals in these same groups. All control, 1X, 3X, and 5X animals were free of cosmetic effects by day 2, 4, 3, or 4, respectively.

3. Mortality: There were no deaths or moribund sacrifices during the study.

C. BODY WEIGHT AND WEIGHT GAIN: Selected body weight data are given in Table 4. Statistical analysis of the absolute body weights indicated that there were no significant group*sex*day or group*day interactions. There were significant ($p<0.05$) group*sex and sex*day interactions, and the group main effect was significant ($p<0.001$). The results of the statistical analysis of body weight were considered (by the study statistician) inconclusive. Comparison of the mean absolute body weights of the treated male and females to those of controls at each time point did not reveal any dose- or treatment-related differences, but the 5X animals of both sexes had treatment-related decreases in body weight gain relative to their respective controls during days -1 to 7. Differences in body weight gain during days -7 to -1, were not treatment-related and are likely due to individual difficulties with weaning.

D. FOOD CONSUMPTION: Selected food consumption data are given in Table 5. Three to seven puppies per group consumed the entire ration on most of the days of the study. The 5X animals had biologically and statistically significantly lower mean food consumption than controls on days 1-5, and nine of the puppies in this group consumed less than 100 grams of food on at least one day during the period from Day 1 to Day 9 (Table 6). This drop in food consumption correlates with the decreased body weight gain by the animals in this group during days -1 to 7.

TABLE 4: Body weight data from puppies treated with 104.5 or 104.05 Placebo (kg) [a]					
Parameter/ Study day or interval		Dosage			
		Control	1X	3X	5X
Males					
Absolute body weight:	**Day -14**	1.63±0.47	1.47±0.30	1.58±0.40	1.87±0.50
	Day -7	2.00±0.53	1.85±0.30	2.00±0.38	2.23±0.42
	Day -1	2.10±0.45	2.17±0.41	2.33±0.33	2.50±0.51
	Day 7	2.45±0.46	2.55±0.51	2.72±0.38	2.67±0.72
	Day 14	2.67±0.47	2.75±0.53	2.93±0.35	2.83±0.61
Body weight gain [b]:	**Days -14 to -7**	0.37	0.38	0.42	0.36
	Days -7 to -1	0.10	0.32	0.33	0.27
	Days -1 to 7	0.35	0.38	0.39	0.17 (-51) [c]
	Days 7 to 14	0.22	0.20	0.21	0.16
Females					
Absolute body weight:	**Day -14**	1.65±0.14	1.57±0.33	1.70±0.13	1.47±0.24
	Day -7	2.02±0.17	1.82±0.34	2.08±0.19	1.78±0.13
	Day -1	2.33±0.29	2.02±0.38	2.37±0.25	1.97±0.12
	Day 7	2.73±0.33	2.33±0.41	2.73±0.33	2.15±0.29
	Day 14	2.98±0.40	2.63±0.44	2.98±0.37	2.48±0.27
Body weight gain [b]:	**Days -14 to -7**	0.37	0.25	0.38	0.31
	Days -7 to -1	0.31	0.20	0.29	0.19
	Days -1 to 7	0.40	0.31	0.36	0.18 (-55)
	Days 7 to 14	0.25	0.30	0.25	0.33

[a] Data derived from Table 73, p. 189, MRID 48467118. Values are Mean ± Standard Deviation, with n=6 for all groups.

[b] Calculated by reviewer, using group mean values; not analyzed statistically.

[c] Numbers in parentheses equal percent different from control; calculated by reviewer.

TABLE 5: Selected food consumption data (g/day, with sexes combined) from puppies treated with 104.5 or 104.05 Placebo[a]				
Study day	Dosage			
	Control	1X	3X	5X
Day -1	354±68	341±89	386±39	321±78
Day 0	329±73	326±88	374±51	296±100
Day 1	336±87	280±119	344±72	209±132 ** (-38%)[b]
Day 2	325±68	309±106	343±99	163±147 ** (-50%)
Day 3	328±96	309±118	360±69	182±145 ** (-45%)
Day 4	333±94	327±95	361±67	226±130 ** (-32%)
Day 5	353±95	361±59	378±38	235±145 ** (-33%)
Day 6	341±97	338±101	383±47	270±146 (-21%)
Day 7	366±72	338±76	401±1	316±132 (-14%)
Day 8	359±73	347±81	397±11	298±138 (-17%)
Day 9	374±42	359±61	389±30	331±115 (-12%)
Day 10	371±53	359±59	390±27	375±63
Day 11	376±39	358±59	401±1	363±73

[a] Data derived from Tables 75, 76, and 79, pp. 191, 192, and 194-196, MRID 48467118. Values are Mean ± Standard Deviation, with n=12 for all groups.

[b] Numbers in parentheses equal percent different from control; calculated by reviewer.

* Statistically different ($p<0.05$) from the control.

** Statistically different ($p<0.01$) from the control.

TABLE 6: Number of puppies in each group (sexes combined) consuming less than 100 g of food on that given day[a]				
Study day	Dosage			
	Control	1X	3X	5X
Day -1	0	0	0	0
Day 0	0	0	0	0
Day 1	0	1	0	2
Day 2	0	0	1	7
Day 3	0	1	0	6
Day 4	0	0	0	1
Day 5	0	0	0	3
Day 6	0	0	0	3
Day 7	0	0	0	1
Day 8	0	0	0	2
Day 9	0	0	0	1
Day 10	0	0	0	0
Day 11	0	0	0	0

[a] Data derived from Table 6 p. 56 of MRID 48467118, with n=12 for all groups.

E. BLOOD ANALYSES:

1. **Hematology:** About two animals per group had normocytic normochromic or microcytic hypochromic anemia on day -7. There were no treatment-related effects on erythrocyte parameters, including Heinz body formation. A reported decrease in mean MCV in 5X animals on day 7 relative to controls was not significant at $p<0.05$ and was of insufficient magnitude to be considered biologically significant.

   A statistically significant increase in the mean leukocyte count of the 5X animals on day 7 was primarily due to two individual values (from puppies #36094 and #87310) outside the reference ranges. The affected animals were among those that exhibited abnormal clinical signs, suggesting that the abnormal observations in these particular animals may have been at least partly due to infection. A statistically significant increase in the mean monocyte count of the 5X animals on day 7 was primarily due to one individual value (from #40074) outside the reference range. The affected animal was treated with dexamethazone on day 3, and the monocytosis may have been the result of that treatment. Statistically significant group*sex*day, group*sex, and/or group*day interactions or group main effects with significant differences at individual time points were noted for some parameters. Comparison of the mean values of the treated groups to those of controls at each time point did not reveal any biologically or statistically significant differences, or where a statistically significant difference was found it was not considered treatment-related due to the absence of a dose response. A reported increase in mean basophil count in 5X animals on day 7 relative to controls was not significant at $p<0.05$ and was of insufficient magnitude to be considered biologically significant.

2. **Clinical Chemistry:** A statistically significant increase in the mean potassium concentration of the 5X group relative on day 7 (5.32 ± 0.53 mmol/L vs. 4.72 ± 0.37 mmol/L for controls; $p<0.01$) was considered potentially treatment-related but non-adverse, as the group mean and all but one individual value fell within the provided reference range.

   There were statistically significant group*sex*day, group*sex, and/or group*day interactions, or group main effects for some parameters, including urea, creatinine, and inorganic phosphate concentrations, but comparison of the mean values of the treated groups to those of controls at each time point did not reveal any biologically or statistically significant differences. Mean sodium concentration was reported as decreased in 5X animals on day 1 and increased in 5X animals on day 7, but these differences were significant at $p<0.10$.

3. **Thyroid function evaluation:** Selected results of the thyroxin (T4) and thyroid stimulating hormone (TSH) assays are given in Table 7. No clear treatment-related effect on thyroid function was seen. It must be noted that, for both parameters, the data were quite variable, with high standard deviations in many cases. However, all group mean values for both parameters and all individual TSH concentrations were within the reference ranges (T4: 10.3-39.0 nmol/L for males and 12.4-43.3 nmol/L for females; TSH: <0.800 ng/mL for males and <0.56 ng/mL for females). Some of the individual T4 concentrations were above or below the reference range; however, there were no correlated increases in TSH for the low values, and no dose- or treatment-related pattern was evident. A statistically significant increase in T4 concentration in 1X animals on day 1 relative to controls was not considered treatment-related due to the absence of a dose response.

TABLE 7: Thyroxin (T4) and thyroid stimulating hormone (TSH) concentrations in beagle puppies treated with 104.5 or 104.05 Placebo (with sexes combined) [a]					
Study day		Dosage			
		Control	1X	3X	5X
T4 (nmol/L):	Day -7	31.5±5.1	31.3±8.4	28.7±8.6	32.6±7.6
	Day 1	22.4±7.7	30.8±7.0 **	25.9±9.0	23.0±7.6
	Day 7	18.5±5.9	19.3±9.1	16.8±7.1	23.7±7.6
	Day 14	16.1±6.7	17.5±8.6	13.9±6.1	18.1±7.1
TSH (ng/mL):	Day -7	0.15±0.04	0.15±0.01	0.17±0.06	0.14±0.00
	Day 1	0.17±0.06	0.15±0.03	0.16±0.04	0.15±0.01
	Day 7	0.15±0.01	0.15±0.01	0.16±0.03	0.17±0.06
	Day 14	0.17±0.06	0.15±0.02	0.14±0.01	0.17±0.06

[a] Data taken from Tables 68 and 70, pp. 184 and 186, MRID 48467118. Values are Mean ± Standard Deviation, with n=12 for all groups, except n=11 for T4 analyses of 1X group on day 7 and controls on day 14.

* Statistically different ($p<0.05$) from the control.

** Statistically different ($p<0.01$) from the control.

F. **GROSS PATHOLOGY:** An animal that died during the acclimation of set 3 was submitted for gross necropsy. The following gross lesions were noted: slight congestion of the mucosa of the duodenum, jejunum, ileum, and colon; hemorrhages and necrosis of the lung tissues; reddish froth in the trachea; hemorrhagic lesions in the bronchial lymph node; and pale appearance of the spleen. Based on these findings, the animal was diagnosed with pneumonia.

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that topical application of the test substance, 104.05, at 1X and 3X the intended dosing volume was generally well tolerated; however, the serious episodes of abnormal clinical signs in two puppies treated at 5X were considered potentially treatment-related and indicative that topical application of the test substance at 5X the intended dosing volume was not well tolerated.

B. **REVIEWER COMMENTS:** Guideline OPPTS 870.7200 states that the animals should be free of infectious diseases, which could complicate the interpretation of the study results. In this study, one animal tested positive for coccidia while abnormal feces consistent with coccidia (i.e. mucoid or loose with mucus and/or frank blood) were seen in what appeared to be a dose-related manner. One animal that died during the week prior to treatment had pneumonia, and during the study one 5X animal had serious respiratory disease requiring the administration of oxygen. Baseline blood work revealed that about two animals per group had normocytic normochromic or microcytic hypochromic anemia on day -7, and one animal had leukopenia. Blood work done on day 7 suggested that the abnormal observations in two 5x animals with serious abnormal clinical signs may have been at least partly due to infection.

Effects were seen that were dose-related. There were increased incidences of vomiting and abnormal feces in 5X animals, and 5X animals of both sexes had decreased weight gain during days -1 to 7, along with decreased food consumption during days 1 through 5. Although it is not possible to know to what extent the compromised health status of the animals contributed to the expression of these effects, special attention must be called to the abnormal neurological signs

seen in this study, which included salivation, ataxia, inability to walk properly, trismus (inability to properly open the mouth), circling, head pressing, seizures, and retropulsion of the neck, which must be considered due to exposure to the formulation.

Because of the severe effects observed in the 5X group, an adequate margin of safety was not established and this study is considered unacceptable to support the use of this product on 8 week old puppies at the proposed dose of 1 mL for puppies weighing up to 22.9 lbs.

C. ADDITIONAL STUDY DEFICIENCIES:

These include the following:

- Some of the puppies may have had a compromised health status. One animal that died during the week prior to treatment had pneumonia. Baseline blood work revealed that 1-2 animals per group had normocytic normochromic or microcytic hypochromic anemia on day -7, and one animal had leukopenia. Blood work done on day 7 suggested that the abnormal observations in two 5X animals with serious abnormal clinical signs may have been at least partly due to infection.
- The product was applied from the base of the head to the rump area, whereas the proposed label says that the product should be applied at a single site in small dogs and puppies 8 weeks old or older and weighing up to 22.9 lbs.
- All groups were not represented in some of the replicates.

IV. REFERENCES:

Anonymous (2011) Summary of companion animal safety data for Effitix™ Topical Solution for Dogs (Fipronil 6.01% and Permethrin 44.88% end use product). Virbac, 1ère Avenue, 06511 Carros Cedex, France. Study number Virbac 104.05-2, April 10, 2011. MRID 48467119. Unpublished.

DATA EVALUATION RECORD

PERMETHRIN; FIPRONIL
[EFFITIX™ TOPICAL SOLUTION FOR DOGS / 104.05]

STUDY TYPE: COMPANION ANIMAL SAFETY STUDY- PUPPIES; OPPTS 870.7200
MRID 48487302

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Risk Assessment Branch VII, Health Effects Division (7509P) Date: 10/7/2011

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety Study - Puppies; OPPTS 870.7200

PC CODES: 109701, 129121 **DP BARCODE:** 390818

TEST MATERIAL (PURITY): 104.05 [6.71 g/100 mL Fipronil and 50.26 g/100 mL Permethrin; Batch No. CGA 09007-1 (T3MOIS 5° C)]

SYNONYMS: Effitix™ Topical Solution for Dogs

CITATIONS: Gupta, S. (2010) A 14-day tolerance study in beagle pups when administered 104.05 (6.7% Fipronil and 50% Permethrin topical solution) topically at 1X and 5X the recommended dose. Charles River Laboratories Preclinical Services Ireland Ltd., Carrentrilla, Ballina, Co. Mayo, Ireland. Study Number F004\09-001, March 12, 2010. MRID 48487302. Unpublished.

SPONSOR: Virbac S.A., Pre-clinical and Clinical Unit (VB7), 13eme Rue Lid - B.P. 27, 06511 Carros Cedex, France.

EXECUTIVE SUMMARY: In a 14-day companion animal safety study (MRID 48487302), 104.05 [6.71 g/100 mL Fipronil and 50.26 g/100 mL Permethrin; Batch No. CGA 09007-1 (T3MOIS 5° C)] was applied topically to the skin on the dorsal midline from the base of the head to the mid back (this is inconsistent with the proposed label which states the entire applicator contents should be squeezed onto the dog's skin at a single site for small dogs and puppies 8 weeks or older weighing up to 22.9 lbs). Groups of six male and six female 52-56 day old (approximately 8-week-old, weighing from 1,5 to 3.5 kg) beagle puppies were treated at 1X (1.0 mL/puppy) or 5X (5.0 mL/puppy) the total recommended dosing volume for the end use product in puppies weighing less 10 kg. "104.05 Placebo" was applied in identical manner to a control group of 6 male and 6 female animals at a dosing volume of 5.0 mL/puppy. The 1X puppies were treated once; the 5X and placebo puppies received five doses of 1.0 mL at approximately 1 hour intervals. Animals were treated on day 0 and observed for 14 days.

One 5X female exhibited profuse salivation on the morning of day 3, exhibited ataxia, generalized tremors, "dullness," and lateral recumbency on days 3-4, and was subsequently euthanized for humane reasons on day 4. There were no gross or microscopic findings to account for the neurological signs; chronic active inflammation with hemorrhage was present in a localized area of one lung, but the study pathologist did not consider these changes extensive enough to cause clinical signs. The 5X males gained less weight than controls during days -1 to 7 (49% less than controls), and 5X animals of both sexes had biologically and statistically significantly decreased mean food consumption on days 1-3 (25-29% less than controls; $p<0.01$). Transient cosmetic effects such as clumping and a greasy appearance of the hair coat, with or without deposits, matting, or spiking were noted within one hour

of the first application and resolved by day 5 at all dose levels. There were no treatment-related effects on hematology, clinical chemistry, or coagulation parameters, or serum thyroxin and thyroid stimulating hormone concentrations.

Toxicity was evident at the 5X dose level as abnormal neurological clinical signs (ataxia, generalized tremors, and profuse salivation) were observed in one female along with decreased food consumption in both sexes on Days 1 through 4 and decreased body weight gain in males. therefore, an adequate margin of safety has not been demonstrated in 8-week-old puppies.

This companion animal safety study in 8 week old puppies does not demonstrate an adequate margin of safety and is classified as **Unacceptable/Guideline.** It **does not satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in juvenile dogs. It should be noted that this limit test preceded a later full study in puppies (MRID 48467118).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided for the study report (MRID 48487302). Signed and dated GLP and Data Confidentiality statements were provided for the safety summary (MRID 47914234); the GLP Compliance Statement consisted of a declaration that this volume "is not subject to GLP certification" because no study was being submitted.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: 104.05 [End-use Product: Effitix™ Topical Solution for Dogs]

Description:	Clear, slightly yellow solution
Batch #:	CGA 09007-1 (T3MOIS 5° C)
Purity:	6.71 g/100 mL Fipronil and 50.26 g/100 mL Permethrin
Compound Stability:	Expiration date: December 2009; considered stable until that date, stored in original packaging, at 16-26° C.).
CAS #:	Not Provided

2. Vehicle control: 104.05 Placebo

Description:	Clear solution
Batch #:	NDE 09132
Purity:	0.02% (w/v) Butylhydroxyanisole, 0.01% (w/v) Butylhydroxytoluene, and Ethylene diethylene glycol (QSP 100 mL)
Compound Stability:	Expiration date: September 2009; considered stable until that date, stored in original packaging, at 16-26° C.).
CAS #:	Not Provided

3. Positive control: No positive control was used.

4. Test animals:

Species:	Dog	
Breed:	Beagle	
Age/weight at study initiation:	52-56 days old/ Males: 1.5-3.5 kg (on day -1); Females: 1.6-3.1 kg (on day -1)	
Source:	Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Co. Mayo, Ireland	
Housing:	Prior to weaning (day -7): puppies were housed with dams in two adjoining pens (each 1.7 m x 1.4 m) with the dividing gate opened, except during daily 2- to 3-hour intervals, during which the dam was separated from the puppies to prepare them for weaning; Days -7 through -3: puppies were housed in groups of two or three; Days -2 through 14: puppies were housed individually in pens measuring 1.7 m x 1.4 m. Infrared lamps were provided.	
Diet:	Pedigree pup food (Pedigree Masterfoods, Melton Mowbray, Leicester, U.K.), approximately 400 g/pup/day Supplemental food (e.g. Welpi® milk replacer) was offered to pups when deemed necessary.	
Water:	*Ad libitum* potable water via automatic drinkers or stainless steel bowls	
Environmental conditions:	Temperature: Humidity: Air changes: Photoperiod:	15-19° C. 49-65% Not reported Not reported
Acclimation period:	Fourteen days.	

B. STUDY DESIGN:

1. In life dates: Start: July 13, 2009; End: October 19, 2009.

2. **Animal assignment:** Study design is given in Table 1. The study was conducted in nine replicates, as pups of the appropriate age became available. On day -1, the animals from each replicate were assigned to groups according to body weight, using a stratified randomized block design. All pups meeting the inclusion criteria were ranked within sex in order of decreasing body weight, with any same-sex pups of identical body weight ranked in order of decreasing microchip number. To the extent possible, blocks of three same-sex pups were formed and then randomly allocated to study groups using random order numbers derived from Fisher and Yates tables. When necessary, an incomplete block would be completed using pups from the subsequent set. Table 2 lists the number of pups in each set that were assigned to each group. The study was not blinded.

TABLE 1: Study design [a]

Test Group	Dosing volume (mL/puppy)	Dose (mg/puppy)		Dose (mg/kg) [b]		Number assigned	
		Fipronil	Permethrin	Fipronil	Permethrin	Males	Females
1. Control	5 mL (5 applications of 1.0 mL of vehicle control)	0	0	0	0	6	6
2. 1X	1 mL (1 application of 1.0 mL of the test item)	67.1	502.6	19.2-39.5	143.6-295.6	6	6
3. 5X	5 mL (5 applications of 1.0 mL of the test item)	335.5	2513	101.7-176.6	761.5-1323	6	7 [c]

[a] Data taken from pp. 23 and 39, MRID 48487302.

[b] Calculated by reviewer, using day -1 body weight ranges of 1.7-3.5 kg and 1.9-3.3 kg for the 1X and 5X groups, respectively.

[c] An additional animal was assigned following the moribund sacrifice of one animal in this group.

TABLE 2: Study design [a]

Test Group	Sets								
	1	2	3	4	5	6	7	8	9
1. Control	2 F	1 M, 1 F	2 M, 1 F	1 F	--	1 F	1 M	2 M	--
2. 1X	1 M, 2 F	1 M, 1 F	1 M	1 M	1 M	1 M, 2 F	1 F	--	--
3. 5X	2 F	1 M, 1 F	1 M, 1 F	1 M, 1 F	1 M, 1 F	1 M	1 M	--	1 F

[a] Data compiled by reviewer using Table 1, p. 38, MRID 48487302.
M = male; F = female.

3. **Dose selection rationale:** According to the study report, a 1-mL dosing volume is the normal recommended dose for this product for dogs, and presumably for puppies, weighing less than 10 kg. The study author stated that the "multiple" of the recommended dose was required by OPPTS 870.7200. The vehicle control substance was also administered at 5 times the normal recommended dosing volume of the product. The exaggerated doses were achieved via five applications of the end-use product or the control item (at approximately one hour intervals). [redacted]. It should be noted that this limit test preceded a later full study in puppies (MRID 48467118).

Inert ingredient information may be entitled to confidential treatment

4. **Treatment:** The control or test material, as appropriate, was applied topically on day 0, using a syringe without a needle. For each application, the tip of the syringe was positioned on the dorsal cervical area at the base of the pup's head and used to separate the pup's hair so the material could be applied at the skin level, and the contents of the syringe were then applied, as evenly as possible, from the base of the head to the mid back. Following application, the pup was restrained in an upright position for at least two minutes to prevent run-off of the test or control substance. Syringe volumes were visually confirmed immediately prior to administration, and each syringe was checked after administration to ensure that none of the contents remained. To achieve the exaggerated 5x doses, the control or test material was applied on five occasions with 1 hour (± 5 minutes) between each application. There was no evidence of run-off

5. Statistics:

Descriptive statistics were generated for all endpoints (separately by sex and combined) at each time point.

Body weight and food consumption, hematology and clinical chemistry parameters, and thyroxin and thyroid stimulating hormone values were analyzed using repeated measures analysis of covariance (RMANCOVA) including treatment, sampling day, sex, and the interaction terms "treatment by sampling day (group*day)," "treatment by sex" (group*sex), "sex by sampling day" (sex*day), and "treatment by sex by sampling day" (group*sex*day) as fixed effects. The set (replicate) was also included in the model as a fixed factor but was only retained if significant ($p<0.05$). The individual animal was identified as the subject in the repeated statement. The covariate was the pretreatment baseline measurement or the average of the three pretreatment baseline measurements in the case of body weight.

For each analysis, the appropriate variance-covariance matrix structure was selected from among compound symmetry, heterogeneous compound symmetry, first-order autoregressive, and heterogeneous first-order autoregressive, based on the Akaike Information Criterion.

If the group*sex*day interaction was significant ($p<0.05$), then the statistical analysis was considered inconclusive. If the group*sex*day interaction was not significant, the interactions of group*sex and group*day were evaluated. If group*sex was significant at $p<0.05$ but group*day was not significant ($p>0.10$), then the statistical analysis was considered inconclusive. If group*day was significant at $p<0.10$, pair-wise comparisons of each treated group least squares mean was performed against the control group least squares mean at each sampling day, using a two-sided Student's t-test.

When the group*sex, group*day, and group*sex*day interactions were not significant, the "treatment" main effect was evaluated at $p<0.10$. If significant, pair-wise comparisons of each treated group least squares mean was performed against the control group least squares mean, using a two-sided Student's t-test. If not significant, no further analyses were conducted on the variable.

Profile plots were provided for all continuous variables and included baselines (or arithmetic means of pre-study data) and all data collected from day 1 through the end of the study. For each endpoint, the individual data were presented separately for each treatment group (with the sexes

combined), and group mean values (for the sexes combined) were presented together, on a single plot.

Potential outliers were verified with the study director, and no outliers were excluded. The following defaults were used for the analyses: creatinine values recorded as "<18" were defaulted to 18; total and direct bilirubin values recorded as "<1.7" were defaulted to 1.7; and thyroid stimulating hormone values recorded as "<0.14" were defaulted to 0.14.

The clinical signs data were not subjected to statistical analysis. The planned statistical analysis of death or sacrifice via logistic regression was not conducted because only one animal was sacrificed.

C. **METHODS:**

1. **Observations:**

a. **General health observations:** Beginning on day -14 and continuing through day -1, general health observations were recorded once daily. No further details were provided concerning the evaluated parameters or whether the evaluations were cage-side or hands-on.

b. **Clinical assessments:** All pups were examined by a veterinarian on days -14 and -1. During the study, a veterinarian conducted clinical assessments on all animals prior to the first treatment and at 1 hour (±5 minutes), 2, 3, 4, and 5 hours (±10 minutes), and 6, 7, and 8 hours (±30 minutes) after the final treatment on day 0. For the control and 5X animals, clinical assessments were also performed within 10 minutes prior to the second, third, fourth and fifth treatment. During the remainder of the study interval (days 1-14), clinical assessments were performed by a veterinarian twice daily, once in the morning and once in the afternoon, with at least four hours between assessments. Clinical assessments consisted of observing each animal for at least one minute and recording the presence or absence of the following: lethargy, ataxia, recumbency, paralysis, coma, pruritis, hyperactivity, tremors, convulsions, abnormal mydriasis, abnormal miosis, corneal opacity, dyspnea, tachypnea, coughing, abnormal salivation, vomiting, abnormal mucous membranes, ocular discharge, nasal discharge, cardiovascular changes, abnormal feces, abnormal urine, abnormal coat condition, and abnormalities of the application site. For any finding that was present, a brief comment further describing the condition was made at the first point of detection and/or at other points of detection.

2. **Body weight:** The animals were weighed on days -14, -7, -1, 7, and 14.

3. **Food consumption:** From day -2 through day 13, each puppy was offered a pre-weighed, approximately 400-g quantity of food, and, on the following day, unconsumed food was removed from the pen and weighed.

4. **Clinical Pathology:** Each animal had blood collected for hematology, clinical chemistry, and thyroid function evaluation on day -7, day 1 (24 hours ± 2 hours after the first application), and day 7, and blood was collected for thyroid function evaluation on day 14. On days -7, 1, 7, and 14, food was not offered to the animals until after blood sampling was performed, but there was no mention of withholding food and/or water for a specific duration of time prior to collection, and the venipuncture site also was not reported. The CHECKED (X) parameters were examined.

a. **Hematology:**

X	Hematocrit (HCT)*	X	Leukocyte differential count* (absolute)
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		Morphology (if indicated)
X	(Thromboplastin time)*	X	Heinz body formation
	(Clotting time)		
X	(Prothrombin time)*		

* Recommended for companion animals safety evaluation based on OPPTS 870.7200

b. **Clinical Chemistry:**

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Urea nitrogen (BUN)*
X	Phosphorus*		Cholesterol
X	Potassium*	X	Globulins*
X	Sodium*	X	Glucose*
	ENZYMES	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Direct bilirubin*
	Cholinesterase (ChE)		Indirect bilirubin
	Creatine phosphokinase	X	Total protein (TP)*
	Lactic acid dehydrogenase (LDH)		Triglycerides
X	Alanine aminotransferase (ALT/also SGPT)*		Serum protein electrophoresis
X	Aspartate aminotransferase (AST/also SGOT)*		Albumin/globulin ratio
	Sorbitol dehydrogenase		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Recommended for a companion animal safety evaluation based on OPPTS 870.7200.

c. **Thyroid Function:** Serum thyroxin and thyroid stimulating hormone assays were done using canine-specific radioactive immunoassays (Siemens), with the results counted using a gamma counter. The separated serum was stored at between -15° C and -30° C until shipment on dry ice to the analyzing laboratory (Charles River Laboratories, Central Laboratory Services, Edinburgh, U.K.).

5. **Urinalysis:** Urinalysis is not required for companion animal safety studies and was not done as part of the current study.

6. **Sacrifice and Pathology:** Terminal sacrifices and gross necropsies were not done and are not required under OPPTS 870.7200. One animal was sacrificed moribund during the study and subjected to gross necropsy. The indicated (X) organs or representative samples thereof were collected, preserved in neutral buffered formalin, processed, and examined microscopically.

X	DIGESTIVE SYSTEM
	Tongue
	Salivary glands
X	Esophagus
X	Stomach (fundic, gastric, pyloric)
X	Duodenum
X	Jejunum
X	Ileum
X	Cecum
X	Colon
	Rectum
X	Liver
	Gall bladder
	Bile duct
X	Pancreas
	RESPIRATORY
	Trachea
X	Lung
	Nose
	Pharynx
	Larynx

X	CARDIOVASC./HEMAT.
	Aorta and carotid arteries
X	Heart
X	Bone marrow
	Lymph nodes
X	Spleen
X	Thymus
	UROGENITAL
X	Kidneys
X	Urinary bladder
	Testes
	Epididymides
	Prostate
	Seminal vesicles
X	Ovaries
X	Uterus
	Vagina

X	NEUROLOGIC
X	Brain
X	Peripheral nerve (sciatic)
X	Spinal cord
	Pituitary
X	Eyes
	GLANDULAR
X	Adrenal gland
X	Parathyroid
X	Thyroid
	OTHER
	Bone (femur)
	Skeletal muscle
X	Skin (application site and untreated skin)
	Gross lesions and masses (selected)

II. RESULTS

A. **ACTUAL DOSES ADMINISTERED:** The mg/kg doses of the active ingredients are given in Table 1.

B. **OBSERVATIONS:**

1. **Mortality:** One 5X female (animal #63312) was euthanized for humane reasons on day 4.

2. **Clinical signs of toxicity:** No abnormalities were noted during the "general health observations" conducted between day -14 and day -1. One 5X female (animal #63312) exhibited profuse salivation on the morning of day 3, exhibited ataxia, generalized tremors, "dullness," and lateral recumbency on days 3-4, and may have shown signs of pain on day 4 (it was unclear from the study report); this animal was subsequently euthanized for humane reasons on day 4.

   The only other reported abnormal clinical signs were abnormal feces, i.e. slightly loose feces, mucoid feces, and/or fresh blood and/or mucus in feces. Three to four animals per group exhibited abnormal feces on at least one occasion during the study, most commonly prior to the first treatment on day 0.

3. **Local effects at the dose sites:** Within one hour of the first application, all of the animals had clumping and a greasy appearance of the hair coat, with or without additional findings such as deposits, matting, or spiking. All control and 1X animals were free of cosmetic effects by day 2, and all 5X animals were free of cosmetic effects by day 5.

C. **BODY WEIGHT AND WEIGHT GAIN:** Body weight data are given in Table 3. Statistical analysis of absolute body weight indicated that there were no significant group*sex*day, group*day, or group*sex interactions, and the group main effect also was not significant. The 5X males gained less weight than controls during days -1 to 7, but a similar difference was not seen in females.

TABLE 3: Body weight data from puppies treated with 104.5 or 104.05 Placebo [a]

Parameter/ Study day or interval		Dosage		
		Control	1X	5X
Males				
Absolute body weight:	Day -14	1.72±0.15	2.03±0.58	1.85±0.46
	Day -7	2.12±0.29	2.50±0.53	2.27±0.50
	Day -1	2.38±0.23	2.82±0.49	2.53±0.60
	Day 7	2.75±0.14	3.13±0.49	2.72±0.58
	Day 14	3.08±0.19	3.38±0.48	2.98±0.58
Body weight gain [b]:	Days -14 to -7	0.40	0.47	0.42
	Days -7 to -t	0.26	0.32	0.26
	Days -1 to 7	0.37	0.31	0.19 (-49) [c]
	Days 7 to 14	0.33	0.25	0.26
Females				
Absolute body weight:	Day -14	1.60±0.35	1.55±0.21	1.73±0.42
	Day -7	1.92±0.45	1.83±0.34	2.09±0.42
	Day -1	2.10±0.48	2.10±0.42	2.39±0.38
	Day 7	2.52±0.39	2.37±0.33	2.75±0.40
	Day 14	2.75±0.36	2.60±0.33	3.03±0.39
Body weight gain [b]:	Days -14 to -7	0.32	0.28	0.36
	Days -7 to -1	0.18	0.27	0.30
	Days -1 to 7	0.42	0.27	0.36
	Days 7 to 14	0.23	0.23	0.28

[a] Data derived from Table 74, p. 207, MRID 48487302. Values are Mean ± Standard Deviation, with n=6 for all groups, except n=7 for 5X females on days -14 through -1.

[b] Calculated by reviewer using group mean values.

[c] Numbers in parentheses equal percent different from control; calculated by reviewer.

D. **FOOD CONSUMPTION:** Selected food consumption data are given in Table 4. Almost all of the puppies consumed the entire ration on most, or even all, of the days of the study. The 5X animals had biologically and statistically significantly lower mean food consumption than controls on days 1-3. A smaller statistically significant decrease in the 1X group on day 1 served to illustrate a dose response pattern and is considered treatment-related but was insufficient magnitude and duration to be considered biologically significant.

The food consumption data are of somewhat limited usefulness because the puppies were not fed *ad libitum* and because, more often than not, most of the puppies consumed all of the food that was offered.

TABLE 4: Selected food consumption data from puppies treated with 104.5 or 104.05 Placebo (g/day, with sexes combined) [a]

Study day	Dosage		
	Control	1X	5X
Day -1	332±128	393±24	360±79
Day 0	384±33	354±67 * (-8%) [b]	356±64
Day 1	391±34	336±78 ** (-14%)	293±110 ** (-25%)
Day 2	379±69	382±64	285±143 ** (-25%)
Day 3	377±69	368±70	269±142 ** (-29%)
Day 4	379±46	369±69	327±139 ** (-14%)
Day 5	386±29	370±67	375±46

[a] Data derived from Tables 76, 77, and 80, pp. 209, 210, and 212-213, MRID 48487302. Values are Mean ± Standard Deviation, with n=12 for all groups, except n=13 for 5X group on days -1 through 4.

[b] Numbers in parentheses equal percent different from control; calculated by reviewer.

* Statistically different ($p<0.05$) from the control.

** Statistically different ($p<0.01$) from the control.

E. BLOOD ANALYSES:

1. **Hematology and coagulation:** There were no treatment-related effects on the evaluated hematology and coagulation parameters. Increased MCV in 1X animals on day 1 relative to controls was not considered treatment-related because a dose response was not evident, and because there were no correlated effects on RBC, HCT, or HGB. Monocyte counts of the 1X and 5X groups were lower than those of controls for the study overall, but the mean values for these groups were within the provided reference range at all time points; the apparent difference was related to higher than normal mean values for controls on days 1 and 7, i.e. mean values that fell outside the provided reference range. Statistical analyses for a number of parameters were considered (by the study author and statistician) to be inconclusive, but all group means were within the provided reference ranges and no dose response patterns were evident.

2. **Clinical Chemistry:** There were no treatment-related effects on any of the evaluated clinical chemistry parameters. There were statistically significant group*sex*day, group*sex, and/or group*day interactions, or group main effects for some parameters, including aspartate amino transferase activity and chloride, sodium, and albumin concentrations, but comparison of the mean values of the treated groups to those of controls at each time point did not reveal any biologically or statistically significant differences.

3. **Thyroid function evaluation:** Selected results of the thyroxin (T4) and thyroid stimulating hormone (TSH) assays are given in Table 5. No clear treatment-related effect on thyroid function was seen. It must be noted that, for both parameters, the data were quite variable, with high standard deviations. However, all group mean values for both parameters and all individual TSH concentrations were within the reference ranges (T4: 10.3-39.0 nmol/L for males and 12.4-43.3

nmol/L for females; TSH: <0.800 ng/mL for males and <0.56 ng/mL for females; MRID 48467118). Some of the individual T4 concentrations were above or below the reference range; however, there were no correlated increases in TSH for the low values, and no dose- or treatment-related pattern was evident.

TABLE 5: Thyroxin (T4) and thyroid stimulating hormone (TSH) concentrations in beagle puppies treated with 104.5 or 104.05 Placebo (with sexes combined) [a]

Study day		Dosage		
		Control	1X	5X
T4 (nmol/L):	Day -7	32.4±12.0	28.2±7.5	30.8±7.9
	Day 1	23.0±8.9	22.7±4.5	24.4±8.0
	Day 7	22.3±9.0	20.3±8.3	20.3±5.2 [b]
	Day 14	17.7±5.6	17.1±7.5	18.1±6.6
TSH (ng/mL):	Day -7	0.20±0.04	0.19±0.09	0.21±0.07
	Day 1	0.16±0.03	0.17±0.04	0.18±0.06
	Day 7	0.17±0.05	0.18±0.06	0.18±0.06 [b]
	Day 14	0.17±0.04	0.15±0.03	0.16±0.02

[a] Data taken from Tables 70 and 72, pp. 203 and 205, MRID 48487302. Values are Mean ± Standard Deviation, with n=12 for all groups, except n=13 for the 5X group on days -7, 1, and 7.

[b] Mean includes results from a sample taken from the moribund 5X female on day 4.

F. SACRIFICE AND PATHOLOGY:

1. **Gross pathology:** The following gross lesions were noted in the 5X animal that was sacrificed moribund on day 4: congestion of the duodenal mucosa; focal congestion in the jejunal mucosa; congested and hemorrhagic lungs; congestion of the thymus; and enlargement of the liver with a firm consistency. There were no findings that correlated with the observations of ataxia, tremors, profuse salivation, dullness, or recumbency.

2. **Microscopic pathology:** Chronic active inflammation with hemorrhage was present in a localized area of one lung as a histopathological correlate to the gross findings in the lungs; however, the pathologist did not consider these changes extensive enough to cause clinical signs. Gram staining was done and found to be negative for bacteria. There were no findings that correlated with the observations of ataxia, tremors, profuse salivation, dullness, or recumbency.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that 104.05 (a combination of 6.7% w/v fipronil and 50% w/v permethrin) was well tolerated both locally and systemically when administered topically to beagle pups at 1X and 5X the recommended dose.

B. REVIEWER COMMENTS: In disagreement with the study author, it is the opinion of the reviewer that toxicity was evident at the 5X treatment level as decreased food consumption in both sexes and decreased body weight gain in males over days -1 to 7. The puppies were not fed *ad libitum* by offering them more food than they were likely to eat, and not feeding *ad libitum*

decreases the likelihood that body weight data accurately reflect an adverse effect. This may be why a similar effect on body weight gain was not seen in females.

The reviewer also disagrees with the study author's conclusion that "inability to cope physiologically following individual housing post-weaning" was the most likely cause of the moribundity of the animal that was sacrificed on day 4, and the neurological signs (ataxia, generalized tremors, and salivation) exhibited by this animal are of particular concern. In a later companion animal safety study, conducted at the same testing laboratory (MRID 48467118), neurological signs were also seen at the 5X dose. These included ataxia, generalized tremors, and salivation along with additional signs such as inability to walk properly, trismus, circling, seizures, and retropulsion of the neck. Although physiological stress and concurrent or prior respiratory disease may have contributed to the moribundity, considering the two studies together, it is concluded that the neurological signs seen in the current study were treatment-related, at least in part. It also must be noted that neurological signs are consistent with the known toxicity of the active ingredients.

Toxicity was evident at the 5X dose level as abnormal neurological clinical signs (ataxia, generalized tremors, and profuse salivation) in one female along with decreased food consumption in both sexes and decreased body weight gain in males; therefore, an adequate margin of safety has not been demonstrated in 8-week-old puppies.

C. <u>STUDY DEFICIENCIES</u>: The following deficiencies were noted:

- The product was applied from the base of the head to mid back, whereas the proposed label says that the product should be applied at a single site in small dogs and puppies 8 weeks old or older and up to 22.9 lbs.
- All groups were not represented in some of the replicates. Replicate 5 had no control group, Replicate 8 had only 2 control animals and Replicate 9 had one 5x female.

IV. REFERENCES

Gupta, S. (2011) A 14-day tolerance study in beagle pups when administered 104.05 (6.7% Fipronil and 50% Permethrin topical solution) topically at 1X, 3X and 5X the recommended dose. Charles River Laboratories Preclinical Services Ireland Ltd., Carrentrila, Ballina, Co. Mayo, Ireland. Study Number F004\10-003, April 6, 2011. MRID 48467118. Unpublished.

Anonymous (2011) Summary of companion animal safety data for Effitix™ Topical Solution for Dogs (Fipronil 6.01% and Permethrin 44.88% end use product). Virbac, 1ère Avenue, 06511 Carros Cedex, France. Study number Virbac 104.05-2, April 10, 2011. MRID 48467119. Unpublished.

ACUTE TOX ONE-LINERS:

1. DP BARCODE: 390818				
2. PC CODES: 109701 (Permethrin), 129121 (Fipronil)				
3. CURRENT DATE: September 27, 2011				
4. TEST MATERIAL: 104.05 (6.71 g/100 mL Fipronil and 50.26 g/100 mL Permethrin; Batch No. CGA 09007-1); described as a clear, slightly yellow solution.				
Study/Species/Lab Study # /Date	**MRID**	**Results**	**Tox. Cat.**	**Core Grade**
Companion Aaimal Safety / adult beagle dog / Huntingdon Life Sciences / Lab Project ID VRB0017 / February 5, 2010	48467117	There were no treatment-related effects on mortality, body weight or body weight gain, food consumption, hematology, clinical chemistry, or coagulation parameters, or serum thyroxin and thyroid stimulating hormone. Treatment at 5X the recommended therapeutic dose resulted in an increased incidence of loose feces within 4 to 8 hours of dosing; three 5X dogs exhibited a total of seven incidences compared to no incidences in coatrols. **It is concluded that the margin of safety in 10- to 20-kg adult beagle dogs administered 104.05 [End-use Product: Effitix™ Topieal Solution for Dogs] is at least 5x the recommended dose (2.0 mL/dog).**	NA	A
Companion Animal Safety / 8 week old beagle dog / Charles River Laboratories Ireland / Lab Study No. F004\110406 / April 6, 2011	48467118	At 5X there were increased incidences of vomiting and abnormal feces, i.e. feces that were liquid, loose, mucoid, with traces of blood, and/or discolored (seen in 4-5 5X animals vs. 0 controls). 5X animals of both sexes had decreased weight gain during days -1 to 7 (51% and 55% less than controls for males and females, respectively). During days 1-5 of the study, the daily food consumption of the 5X animals was 32-50% less than that of controls ($p<0.01$), and there were 26 occasions (involving nine 5X puppies) in the period from Day 1 to 9 when a 5X puppy consumed less than 100 g of food in a single day (this occurred only twice in the 1X group and once in the 3X group during this period). Two 5X animals also exhibited abnormal neurological signs, including salivation, ataxia, inability to walk properly, trismus (inability to properly open the mouth), walking in a circle to the right, resting head against the wall, generalized tremors, one episode of seizures (clonic convulsions), "dullness," and regular retropulsion of the neck in one animal and salivation, ataxia, unsteadiness on hind limbs and gait incoordination due to weakness, and slight generalized tremors in the other animal. This companion animal safety study with 8 week old puppies does not demonstrate an adequate (5X) margin of safety. This study is classified as **Unacceptable/ Guideline.** It does not satisfy the guideline requirement for a companion animal safety study (OPPTS 870.7200) in juvenile dogs.	NA	U

Companion Animal Safety / 8 week old beagle dog / Charles River Laboratories Ireland / Lab Study No. F004\09-001 / March 12, 2010	48487302	One 5X female exhibited profuse salivation on the morning of day 3, exhibited ataxia, generalized tremors, "dullness," and lateral recumbency on days 3-4, and was subsequently euthanized for humane reasons on day 4. There were no gross or microscopic findings to account for the neurological signs; chronic active inflammation with hemorrhage was present in a localized area of one lung, but the study pathologist did not consider these changes extensive enough to cause clinical signs. The 5X males gained less weight than controls during days -1 to 7 (49% less than controls), and 5X animals of both sexes had biologically and statistically significantly decreased mean food consumption on days 1-3 (25-29% less than controls; $p<0.01$). **It is concluded that toxicity was evident at the 5X dose level as abnormal neurological clinical signs (ataxia, generalized tremors, and profuse salivation) were observed in one female along with decreased food consumption in both sexes on Days 1 through 4 and decreased body weight gain in males. therefore, an adequate margin of safety has not been demonstrated in 8-week-old puppies.** This companion animal safety study in 8 week old puppies does not demonstrate an adequate margin of safety and is classified as **Unacceptable/Guideline.** It does not satisfy the guideline requirement for a companion animal safety study (OPPTS 870.7200) in juvenile dogs.	NA	U

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived

Effitix Pup Safety Proposal /2382-RIT
Jim Barron
to:
Bonaventure Akinlosotu
11/08/2011 02:27 PM
Cc:
Richard Gebken, "Brenton Smith", "Terry McNamara", isabelle.villard.external
Hide Details
From: "Jim Barron" <jbarron@exponent.com>

To: Bonaventure Akinlosotu/DC/USEPA/US@EPA

Cc: Richard Gebken/DC/USEPA/US@EPA, "Brenton Smith" <brenton.smith@virbacus.com>, "Terry McNamara" <tmcnamara@exponent.com>, <isabelle.villard.external@virbac.com>

Hi Richard & Byron:
I need your comments/opinion on this "Effitix Pup Safety Proposal", Virbac's rebuttal to our CAS study review.
(*) NOTE: FRIA Date = 11/19/2011 (*)

November 8, 2011

Dear Bonaventure,

Thank you for sending us the Agency's October 13, 2011 review of the companion animal safety studies conducted with Effitix™ Topical Solution For Dogs. Based on the Agency review, the Effitix studies conducted with 8 week old puppies have been classified as Unacceptable/Guideline. Nonetheless, having a puppy claim on the label for this product is very important to Virbac.

Therefore, Virbac is submitting the following proposal based on the supporting justification summarized below:

- ***EPA grant a conditional registration for Effitix Topical Solution For Dogs with a 10 week minimum age limit and a 5 lb minimum weight restriction;***
- ***As a condition of registration, Virbac will conduct and submit to EPA, within 1 year of registration, a new companion animal safety study with 10 week old puppies to confirm product safety.***

The rationale for the above proposal is as follows:

- Fipronil alone spot-on products have an 8 week age limit, and have been used for more than 15 years;
- Permethrin spot-ons have been used for many years, some with even lower minimum age limits; i.e.
    - 4 week age limit (EPA Reg. No. 773 – 73);
    - 7 week age limit for permethrin in combination with imidacloprid (EPA Reg. No. 11556 – 132 to 135 and 11556 – 141 to 144);
    - 7 week age limit for permethrin in combination with dinotefuran (EPA Reg. No. 83399 – 6).
- In the two Virbac Effitix studies on 8 week old pups, there were ***no significant effects*** observed in a total of twenty-four 8 week old pups ***at the 1X dosing***; and;
- There were also ***no significant effects*** observed in the twelve 8 week old pups at the ***3X dosing.***
- ***Significant adverse effects were only seen with 5 of the 24 eight week old pups treated at 5X; no adverse effects were seen at the lower dose levels of 3X and 1X;***
- ***Because of the rapid growth of pups, moving the age limitation from 8 weeks of age to 10 weeks of age and including a 5 lb minimum weight restriction adds additional significant safety factors to the label.***

Thank you for consideration of our proposal. We would be happy to discuss this matter further with the Agency at any time.

Sincerely,

Jim Barron, Ph. D.
Managing Regulatory Consultant
E^xponent®, Inc.
1000 Centre Green Way Suite 200
Cary, NC 27513

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********** ATTACHMENT NOT DELIVERED **********

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For further information, please contact the EPA Call Center at (866) 411-4EPA (4372). The TDD number is (866) 489-4900.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

September 30, 2011

MEMORANDUM

Subject:	Name of Pesticide Product:	EFFITEX TOPICAL SOLUTION FOR DOGS
	EPA Reg. No. /File Symbol:	2382-RIT
	DP Barcode:	DP 390816
	Decision No.:	448350
	Action Code:	R310
	PC Code:	109701 (Permethrin: 44.88%)
		129121 (Fipronil: 6.01%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
9/30/2011

M Hashmi, Ph.D
Sr. Toxicologist

To: Bonaventure Akinlosotu/Richard Gebken RM 10
Insecticide Branch
Registration Division (7505P)

Registrant: VIRBAC AH, INC.

FORMULATION FROM LABEL:

Active Ingredient(s):		by wt.
129121 Fipronil		6.01%
109701 Permethrin		44.88%
Other Ingredient(s):		49.11%
	TOTAL	100.00%

ACTION REQUESTED: The Risk Manager requests:

"For your review: MRID Nos. 484671-11 to 15; for an R310, new fipronil/permethrin containing spot-on for dogs…"

BACKGROUND:

The material received for review includes a set of 5 acute toxicity studies (MRIDs 48467111-48467115); a request for a waiver for the acute inhalation toxicity study; a proposed label (with the signal word CAUTION), a basic CSF (dated March 21, 2011), a cover letter dated April 28, 2011, and a data matrix.

COMMENTS AND RECOMMENDATIONS:

1. A contractor (Summitec Corporation) did the primary reviews on the five acute toxicity studies and produced a DER for each study; TRB did secondary reviews on the DERs, making revisions where appropriate.

2. Four (the acute oral, dermal toxicity, primary eye and primary dermal irritation) of the acute toxicity studies have been classified as acceptable. In addition, TRB recommends for a waiver for the acute inhalation study data requirement, with the product being assigned to EPA Toxicity Category IV by this exposure route.

3. For the dermal sensitization study (MRID 48467115) there was no indication that the test material is a dermal sensitizer. However, the provided positive control study was not conducted within six months of the current study, and the methods used in the positive control study were not described in adequate detail for the reviewer to be able to determine whether the two studies were performed in a similar manner.

4. The following is the acute toxicity profile of 2382-RIT (EFFITEX TOPICAL SOLUTION FOR DOGS) based on the results of the acute toxicity studies, and with designation of the test material as a dermal sensitizer in lieu of an acceptable dermal sensitization study:

Acute oral toxicity	III	Acceptable	MRID 48467111
Acute dermal toxicity	III	Acceptable	MRID 48467112
Acute inhalation toxicity	IV	Waived	
Primary eye irritation	IV	Acceptable	MRID 48467113
Primary dermal irritation	IV	Acceptable	MRID 48467114
Dermal sensitization	Positive[a]	Unacceptable	MRID 48467115

[a]In lieu of an acceptable study, TRB recommends this product be classified as a sensitizer.

5. Based on the acute toxicity profile above, and taking into consideration the proposed uses specified on the label and information in the CSF, the following would be the precautionary and first aid labeling for EPA File Symbol 2382-RIT (EFFITEX TOPICAL SOLUTION FOR DOGS) as obtained from the Label Review System:

PRODUCT ID #: **002382-00187**

PRODUCT NAME: **EFFITEX TOPICAL SOLUTION FOR DOGS**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Harmful if absorbed through skin. Harmful if swallowed. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Wear long-sleeved shirt and long pants, socks, shoes, and gloves. Remove and wash contaminated clothing before reuse.

Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.

First Aid:

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable: - technical information on symptomatology; - use of supportive treatments to maintain life functions; - medicine that will counteract the specific physiological effects of the pesticide; - company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

6. The CSF (dated March 21, 2011) for EPA File Symbol 2382-RIT should also be reviewed and accepted by the TRB Chemistry Team.

DATA EVALUATION RECORD

PERMETHRIN; FIPRONIL
[PROJECT 104.05]

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [OPPTS 870.1100; OECD 423]
ACUTE DERMAL TOXICITY - RAT [OPPTS 870.1200; OECD 402]
ACUTE INHALATION TOXICITY - RAT [OPPTS 870.1300; OECD 403]
ACUTE EYE IRRITATION - RABBIT [OPPTS 870.2400; OECD 405]
ACUTE DERMAL IRRITATION - RABBIT [OPPTS 870.2500; OECD 404]
DERMAL SENSITIZATION - GUINEA PIG [OPPTS 870.2600; OECD 406]
MRID: 48467111, 48467112, 48467113, 48467114, and 48467115

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
Knoxville, Tennessee 37922

Task Order No. 3-B-42

Primary Reviewer:
Donna L. Fefee, D.V.M.

Signature: Donna Fefee, AE
Date: AUG 17 2011

Secondary Reviewers:
Thomas C. Marshall, Ph.D., D.A.B.T.

Signature: Thomas C. Marshall, PE
Date: AUG 17 2011

Robert H. Ross, M.S., Program Manager

Signature: Robert H. Ross
Date: AUG 17 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: Jennifer Goldberg
Date: AUG 17 2011

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Reviewer: Byron T. Backus, Ph.D. **Date:** September 30, 2011
Risk Manager (EPA): 10

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: Project 104.05; 6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch No.: NDE 08301-1; Clear, slightly yellow solution; Density: 1.1125 g/mL; Expiration Date: May 1, 2009; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Rached, E. (2009) Project 104.05: acute oral toxicity study in rats. Study Number C24620. Unpublished study prepared by Harlan Laboratories Ltd., Füllinsdorf, Switzerland. May 15, 2009. 58 p. MRID 48467111.

SPONSOR: Virbac SA, 1ère Avenue 2065 M - LID, BP 27, 06511 Carros Cedex, France.

EXECUTIVE SUMMARY: In a modified acute toxic class method oral toxicity study (MRID 48467111), five groups of three fasted, female HanRcc: WIST(SPF) rats were given single oral gavage doses of undiluted Project 104.05 [6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch #NDE 08301-1] at dose levels of 2000 mg/kg bw (2 groups, steps 1 and 2), 300 mg/kg bw (2 groups, steps 3 and 4), or 500 mg/kg bw (1 group, step 5). The first four "steps" were in accordance with OECD 423. The animals were treated on day 1 and observed for up to 14 days. The animals were 11 weeks old, weighed 170.3-214.8 g, and were supplied by Harlan Laboratories Ltd., Laboratory Animal Services (Füllinsdorf, Switzerland).

The three "step 1" 2000-mg/kg animals were found dead between days 4 and 6, and one "step 2" 2000-mg/kg animal was found dead on day 6. All "step 1" 2000-mg/kg animals had ruffled fur on day 1, at 3-5 hours post-dosing, and did not exhibit any subsequent abnormal clinical signs prior to being found dead on day 4, 5, or 6. All "step 2" 2000-mg/kg animals had ruffled fur, beginning 2 hours after dosing and persisting through death (on day 6) for one animal or through day 12 for the survivors. Additional signs in the "step 2" animals included sedation on days 5 through 6-7 (all 3 animals), reddish, serous nasal discharge in both survivors on day 7, and aggression and vocalization in both survivors between days 6 and 9. No abnormal clinical signs were seen in any of the animals dosed at 300 or 500 mg/kg bw. Almost all of the animals gained weight during both weeks of the study; the exception was one 2000-mg/kg survivor that lost weight during the first week but had a cumulative body weight gain over the entire study interval. Abnormal gross necropsy findings were noted in two 2000-mg/kg animals. These included dark red discoloration of the lungs, gaseous distension of the stomach, reddish or yellowish discoloration of the stomach, small intestines, and cecum (all noted in both of these animals), and reddish discoloration of the colon and rectum (in one animal).

LD_{50} in females > 500 mg/kg bw; < 2000 mg/kg

Based on the acute oral LD_{50} > 500 mg/kg, Project 104.05 is in EPA Toxicity Category III by this exposure route.

This acute oral study is classified as Acceptable. It satisfies the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and [No] Data Confidentiality statements were provided.

RESULTS and DISCUSSION: Individual animals were dosed as follows:

Group / Step	Animal Number	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	1	2000	S	D
	2		S	D
	3		S	D
2	4	2000	S	S
	5		S	S
	6		S	D
3	7	300	S	S
	8		S	S
	9		S	S
4	10	300	S	S
	11		S	S
	12		S	S
5	13	500	S	S
	14		S	S
	15		S	S

S = Survival, D = Death

In the absence of mortality or persistent clinical signs of toxicity, the second group was dosed 48 hours after the second group. Due to the delayed deaths at the initial dose level, subsequent groups were dosed at at least 4-day intervals. The first four "steps" were in accordance with OECD 423; the fifth group of three animals was dosed at 500 mg/kg bw with the stated intention of gaining additional information about the approximate LD_{50} of the test material.

Statistics: Statistical analysis and determination of an exact LD_{50} value were not done and are not required under OPPTS 870.1100 or OECD 423.

A. Mortality: Four of the six animals dosed at 2000 mg/kg bw were found dead (on days 4-6).

B. Clinical observations: The three "step 1" 2000-mg/kg animals had ruffled fur on day 1, at 3-5 hours post-dosing, and did not exhibit any subsequent abnormal clinical signs prior to being found dead on day 4, 5, or 6. The three "step 2" 2000-mg/kg animals had ruffled fur, beginning 2 hours after dosing and persisting through death (on day 6) for one animal or through day 12 for the survivors. Additional signs in the "step 2" animals included sedation on days 5 through 6-7 (all 3 animals), reddish, serous nasal discharge in both survivors on day 7, and aggression and vocalization in both survivors between days 6 and 9. No abnormal clinical signs were seen in any of the animals dosed at 300 or 500 mg/kg bw. Almost all of the animals gained weight during both weeks of the study; the exception was one 2000-mg/kg survivor that lost weight during the first week but had a cumulative body weight gain over the entire study interval.

C. Gross Necropsy: Abnormal findings were noted in two of the decedent, "step 1" 2000-mg/kg animals. These included dark red discoloration of the lungs, gaseous distension of the stomach, reddish or yellowish discoloration of the stomach, small intestines, and cecum (all noted in both of these animals), and reddish discoloration of the colon and rectum (in one animal).

D. Reviewer's Conclusions: It is concluded that in the absence of mortality and symptoms in the three rats dosed at 500 mg/kg the oral LD_{50} can be set at >500 mg/kg. The deaths of 4/6 rats dosed at 2000 mg/kg indicates the LD_{50} < 2000 mg/kg. We can use these findings to assign Project 104.05 to EPA Toxicity Category III by this exposure route.

E. Deficiencies: None.

Reviewer: Byron T. Backus, Ph.D. **Date:** September 30, 2011
Risk Manager (EPA): 10

STUDY TYPE: Acute Dermal Toxicity - Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: Project 104.05; 6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch No.: NDE 08301-1; Clear, slightly yellow solution; Density: 1.1125 g/mL; Expiration Date: May 1, 2009; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Rached, E. (2009) Project 104.05: acute dermal toxicity study in rats. Study Number C24631. Unpublished study prepared by Harlan Laboratories Ltd., Füllinsdorf, Switzerland. March 20, 2009. 53 p. MRID 48467112.

SPONSOR: Virbac SA, 1ère Avenue 2065 M - LID, BP 27, 06511 Carros Cedex, France.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 48467112), a group of five male and five female HanRcc:WIST (SPF) rats was dermally exposed for 24 hours to undiluted Project 104.05 [6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch #NDE 08301-1] at a dose of 2000 mg/kg (=1.80 mL/kg) bw. The doses were applied to clipped application sites on the dorsal trunk (~10% of the body surface area) and covered by a semi-occlusive dressing wrapped around the trunk and secured with an elastic adhesive bandage. The day of application was considered to be day 1, and the animals were observed for 14 days. The animals were supplied by Harlan Laboratories Ltd., Laboratory Animal Services (Füllinsdorf, Switzerland); males were 9 weeks old and weighed 250.5-265.6 g, and females were 11 weeks old and weighed 186.6-195.0 g.

There were no deaths or abnormal gross necropsy findings. There were no abnormal systemic clinical signs in males, and all males gained weight during both weeks of the study. All five females exhibited splayed hind legs between days 2 and 5, and three females exhibited sedation and ventral recumbency on day 2. Two females gained weight during both weeks of the study; the remaining three females lost weight during the first week but had net body weight gain over the cumulative study interval. Erythema was noted on the dose sites of all animals of both sexes on day 2, and one male and one female also had erythema on the dose site on days 6-11. Additional findings on the dose sites included scales and/or crusts, which were noted on three males and four females, with onset on day 6 and resolution prior to day 15 in most cases.

LD_{50} Males > 2000 mg/kg bw
LD_{50} Females > 2000 mg/kg bw
LD_{50} Combined > 2000 mg/kg bw

Based on the acute dermal LD_{50} for males, females, and the combined sexes, Project 104.05 is in EPA Toxicity Category III.

This acute dermal study is classified Acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and [No] Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10

Statistics: Statistical analysis and determination of an exact LD_{50} value were not done and are not required under OPPTS 870.1200 or OECD 402.

A. Mortality: There were no deaths.

B. Clinical observations: There were no abnormal systemic clinical signs in males. All five females exhibited splayed hind legs between days 2 and 5, and three females exhibited sedation and ventral recumbency on day 2. Erythema was noted on the dose sites of all animals of both sexes on day 2, and one male and one female also had erythema on the dose site on days 6-11. Additional findings on the dose site included scales and/or crusts, which were noted on three males and four females, with onset on day 6 and resolution prior to day 15 in most cases. All males and two females gained weight during both weeks of the study; the remaining three females lost weight during the first week but had net body weight gain over the cumulative study interval.

C. Gross Necropsy: There were no abnormal findings.

D. Reviewer's Conclusions: In agreement with the study author, the acute dermal LD_{50} for males, females, and the combined sexes is greater than 2000 mg/kg bw. This places the test material in EPA Toxicity Category III.

E. Deficiencies: None.

Reviewer: Byron T. Backus, Ph.D. **Date:** September 30, 2011
Risk Manager (EPA): 10

STUDY TYPE: Acute Inhalation Toxicity - Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: Effitix™ Topical Solution for Dogs; 6.01% Fipronil, 44.08% Permethrin; End-use product for spot-on use in dogs.

CITATION: Parks, C. (2011) Effitix™ Topical Solution for Dogs (EPA File Symbol 2382-TBA); new product application; waiver request. Study number: not applicable. Unpublished study prepared by Virbac Animal Health, Fort Worth, Texas. April 28, 2011. MRID 48467100.

SPONSOR: Virbac SA, Iere Avenue 2065 M - LID, BP 27, 06511 Carros Cedex, France.

EXECUTIVE SUMMARY: Virbac Animal Health requests a waiver from the requirement to conduct an Acute Inhalation Toxicity study (OPPTS 870.1300). The waiver request is based on the following:

1) The measured vapour pressures of both active ingredients are extremely low. For fipronil it is 2.8×10^{-9} mm Hg at 25° C, and for permethrin it is 2.18×10^{-8} mm Hg at 25° C. The active ingredients are not expected to vaporize from the skin following application, and, thus, will not be available for inhalation.
2) The potential human inhalation exposure to the product is expected to be negligible because only very small amounts of product are applied per application. Application volume depends on the weight of the animal, and the maximum volume to be applied to a single pet at one time is 6.0 mL. The 6.0 mL application volume is recommended only for use on dogs that weigh more than 89 pounds. According to the author, "Therefore, according to the proposed label, a great deal of anticipated product use will occur at much lower volumes on smaller dogs."
3) The method of applying the liquid product directly to the pet creates no particulates, aerosols, or other respirable matter.

In considering this request, the reviewer agrees that non-volatile products, which cannot be readily aerosolized, and which are not heated or diluted to an inhalable state during application are likely waiver candidates. In addition, the Agency has routinely waived the data inhalation study requirement for spot-on products, based on the relatively small quantity of product used and its application directly to the pet.

TRB recommends that the waiver request be granted. The product can be assigned to EPA Toxicity Category IV by this exposure route,

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were *not* provided.

Reviewer: **Byron T. Backus, Ph.D.** **Date:** September 30, 2011
Risk Manager (EPA): 10

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: Project 104.05; 6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch No.: NDE 08301-1; Clear, slightly yellow solution; Density: 1.1125 g/mL; Expiration Date: May 1, 2009; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Rached, E. (2009) Project 104.05: primary eye irritation study in rabbits. Study Number C24653. Unpublished study prepared by Harlan Laboratories Ltd., Füllinsdorf, Switzerland. April 30, 2009. 57 p. MRID 48467113.

SPONSOR: Virbac SA, 1ère Avenue 2065 M - LID, BP 27, 06511 Carros Cedex, France.

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 48467113), 0.1 mL of undiluted Project 104.05 [6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch #NDE 08301-1] was instilled into the conjunctival sac of the unanesthetized left eye of one male and two female New Zealand albino rabbits, and the upper and lower lids were held shut for approximately one second. Eyes were scored for ocular irritation according to the Draize method at 1, 24, 48, and 72 hours and at 7 days after instillation. The untreated right eye of each animal served as a control. The animals were 17 weeks old (male: 2.48 kg; females: 2.69-2.89 kg) and were supplied by Harlan Laboratories B.V. (Horst, the Netherlands).

There were no observations of corneal opacity or iritis. One hour after instillation of the test material, all three treated eyes had conjunctival redness, chemosis, and discharge (scores=1, 1-2, and 1-2, respectively). Conjunctival redness persisted in all three eyes through 72 hours after instillation, and chemosis persisted in one treated eye through 24 hours after instillation. The sclerae of all three treated eyes were slightly reddened at 1 hour and remained reddened in one animal through 48 hours after instillation. No "positive" findings were seen at or after 24 hours, and all eyes were clear of ocular irritation at 7 days. No abnormal systemic clinical signs were recorded. The maximum mean total score (MMTS) was 7.33, recorded one hour after instillation.

In this study, the formulation is mildly irritating. Based on the absence of "positive" findings at or after 24 hours, Project 104.05 is classified as EPA Toxicity Category IV for primary eye irritation.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and [No] Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Observations	Number "positive"/number tested				
	Hours				Days
	1	24	48	72	7
Corneal Opacity	0/3	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3
Conjunctivae:					
Redness *	0/3	0/3	0/3	0/3	0/3
Chemosis *	1/3	0/3	0/3	0/3	0/3
Discharge**	1/3	0/3	0/3	0/3	0/3
Severity of Irritation: Mean Total Score	7.33	2.67	2.00	2.00	0.00

* Score of 2 or more required to be considered "positive."

** Not considered a positive irritation effect; however, scores of 2 or greater are noted here for completeness.

A. Observations: There were no observations of corneal opacity or iritis. One hour after instillation of the test material, all three treated eyes had conjunctival redness, chemosis, and discharge (scores=1, 1-2, and 1-2, respectively). Conjunctival redness persisted in all three eyes through 72 hours after instillation, and chemosis persisted in one treated eye through 24 hours after instillation. The sclerae of all three treated eyes were slightly reddened at 1 hour and remained reddened in one animal through 48 hours after instillation. No "positive" findings were seen at or after 24 hours, and all eyes were clear of ocular irritation at 7 days. No abnormal systemic clinical signs were recorded.

B. Results: The maximum mean total score (MMTS) was 7.33, recorded one hour after instillation.

C. Reviewer's conclusions: The test material is mildly irritating to the eye and (in disagreement with the study author who indicated a Toxicity Category III classification was appropriate) is classified as EPA Toxicity Category IV for primary eye irritation.

D. Deficiencies: None.

Reviewer: Byron T. Backus, Ph.D. **Date:** September 30, 2011
Risk Manager (EPA): 10

STUDY TYPE: Primary Dermal Irritation - Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: Project 104.05; 6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch No.: NDE 08301-1; Clear, slightly yellow solution; Density: 1.1125 g/mL; Expiration Date: May 1, 2009; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Rached, E. (2009) Project 104.05: primary skin irritation study in rabbits (4-hour semi-occlusive application). Study Number C24642. Unpublished study prepared by Harlan Laboratories Ltd., Füllinsdorf, Switzerland. April 30, 2009. 50 p. MRID 48467114.

SPONSOR: Virbac SA, 1ère Avenue 2065 M - LID, BP 27, 06511 Carros Cedex, France.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 48467114), one male and two female New Zealand albino rabbits were dermally exposed to 0.5 mL of undiluted Project 104.05 [6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch #NDE 08301-1] for 4 hours. The doses were applied to intact, clipped application sites on the left flank using a 6.25 cm^2 surgical gauze patch that was held in contact with the skin by an adhesive hypoallergenic semi-occlusive dressing and DermaPlast® restrainer bandage wrapped around the abdomen. The animals were observed for skin reactions at 1, 24, 48, and 72 hours after patch removal, and any irritation at the dose sites was scored according to Draize. The animals were 15-16 weeks old (male: 2.71 kg; females: 2.44-2.78 kg) and were supplied by Harlan Laboratories B.V. (Horst, the Netherlands).

There were no observations of edema. Very slight erythema (score=1) was noted on all three sites one hour after patch removal with resolution within 24 hours of patch removal. No abnormal systemic clinical signs were reported.

In this study, the Primary Irritation Index (PII) is 0.25, and the formulation is a slight irritant. Project 104.05 is classified as EPA Toxicity Category IV for primary dermal irritation.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary skin irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and [No] Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

INDIVIDUAL SKIN IRRITATION SCORES [ERYTHEMA/EDEMA]

Animal No.	Sex	Hours after patch removal			
		0.5-t	24	48	72
81	M	1/0	0/0	0/0	0/0
82	F	1/0	0/0	0/0	0/0
83	F	1/0	0/0	0/0	0/0
Severity of Irritation - Mean Score		1.00/0.00	0.00/0.00	0.00/0.00	0.00/0.00

A. Observations: There were no observations of edema. Very slight erythema (score=1) was noted on all three sites one hour after patch removal with resolution within 24 hours of patch removal. No abnormal systemic clinical signs were reported.

B. Results: The PII is 0.25.

C. Reviewer's Conclusions: The test material is a slight irritant and is classified as EPA Toxicity Category IV.

D. Deficiencies: None.

Reviewer: Byron T. Backus, Ph.D. **Date:** September 30, 2011
Risk Manager (EPA): 10

STUDY TYPE: Dermal Sensitization – Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: Project 104.05; 6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch No.: NDE 08301-1; Clear, slightly yellow solution; Density: 1.1125 g/mL; Expiration Date: May 1, 2009; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Arcelin, G. (2009) Project 104.05: contact hypersensitivity in albino guinea pigs, Buehler test. Study Number C24664. Unpublished study prepared by Harlan Laboratories Ltd., Füllinsdorf, Switzerland. March 20, 2009. 72 p. MRID 48467115.

SPONSOR: Virbac SA, 1ère Avenue 2065 M - LID, BP 27, 06511 Carros Cedex, France.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 48467115), twenty young adult, male, CRL:(HA)BR Dunkin Hartley albino guinea pigs were tested with undiluted Project 104.05 [6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch #NDE 08301-1] using the Buehler method. A separate naïve control group of ten males was treated at challenge only. The animals were 5-7 weeks old, weighed 350-449 g, and were supplied by Charles River Deutschland GmbH (Kisslegg, Germany).

No positive dermal reactions were seen following challenge with the undiluted test material. No abnormal systemic clinical signs were reported, and all of the animals gained weight over the course of the study.

Based on this study, it cannot be determined whether Project 104.05 is a dermal sensitizer.

This study is classified as Unacceptable. It does *not* satisfy the guideline requirement for a primary dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig. The study may be upgraded pending receipt of an adequately reported positive control study, conducted within the appropriate time frame, provided the results are appropriate.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and [No] Data Confidentiality statements were provided.

I. PROCEDURE

A. Induction: The animals were clipped prior to each treatment. For each of three successive weekly inductions, 0.5 mL of the undiluted test material was applied to the left shoulder of each animal using an occlusive 25 mm Hill Top Chamber® and secured in place with adhesive tape wrappings for six hours. Reactions were scored 24 hours post application.

B. Challenge: Twenty-eight days after the first induction, the test animals were challenged with 0.5 mL of the undiluted test material (the highest non-irritating concentration according to preliminary testing), applied to naive sites on the left flank of each animal for 6 hours using the same procedure. Reactions were scored 24 and 48 hours post application.

C. Naive Controls: At challenge, a separate "naive" group of ten previously untreated animals was also treated with 0.5 mL of the undiluted test material. Reactions were scored 24 and 48 hours post application.

II. RESULTS and DISCUSSION:

A. Reactions and duration: No irritation was noted on any of the application sites of the treated animals following any of the induction or challenge doses. Following challenge, no erythema was noted on any of the naïve controls at either time point.

B. Positive control: The study report included the results from a positive control study with alpha-Hexylcinnamaldehyde (RCC Study #B86027), completed on May 5, 2008, which is not within six months of the in-life dates (January 14 to February 19, 2009) of the current study. It cannot be determined whether the induction and challenge procedures used in both studies were similar. One clear difference between the two studies is that two different challenge doses were used in the positive control study.

C. Reviewer's Conclusions: In agreement with the study author, under the conditions of this study, the test material is *not* a dermal sensitizer. However, due to the below-mentioned deficiencies related to the positive control study, the current study is classified as unacceptable and does not satisfy the guideline requirement. The study may be upgraded pending receipt of an adequately reported positive control study, conducted within the appropriate time frame, provided the results are appropriate.

D. Deficiencies: The provided positive control study was not conducted within six months of the current study, and the methods used in the positive control study were not described in adequate detail for the reviewer to be able to determine whether the two studies were performed in a similar manner.

ACUTE TOX ONE-LINERS:

1. DP BARCODE: 390816				
2. PC CODE: 109701, 129121				
3. CURRENT DATE: August 11, 2011				
4. TEST MATERIALS: • Project 104.05 [6.75% (w/v) Fipronil, 49.8% (w/v) Permethrin; Batch #NDE 08301-1] • Effitix™ Topical Solution for Dogs; 6.01% Fipronil, 44.08% Permethrin; End-use product for spot-on use in dogs				
Study/Species/Lab Study # /Date	**MRID**	**Results**	**Tox. Cat.**	**Core Grade**
Acute oral toxicity / rat Harlan Laboratories Ltd. Study #C24620 / May 15, 2009	48467111	LD_{50} in Females > 500 mg/kg, < 2000 mg/kg	III	A
Acute dermal toxicity / rat Harlan Laboratories Ltd. Study #C24631 / March 20, 2009	48467112	LD_{50} Males > 2000 mg/kg LD_{50} Females: > 2000 mg/kg LD_{50} Combined > 2000 mg/kg	III	A
Acute inhalation toxicity / rat Virbac Animal Health No Study # / April 28, 2011	N/a	Waived	IV	W
Primary eye irritation / rabbit Harlan Laboratories Ltd. Study #C24653 / April 30, 2009	48467113	Mildly irritating; MMTS=7.33, at one hour; no positive effects present at or after 24 hours.	IV	A
Primary dermal irritation /rabbit Harlan Laboratories Ltd. Study #C24642 / April 30, 2009	48467114	Slight irritant; PII=0.25; All sites clear of irritation at 24 hours.	IV	A
Dermal Sensitization /guinea pig Harlan Laboratories Ltd. Study #C24664 / March 20, 2009	48467115	No indication of dermal sensitization, but positive control study not within 6 months of this study.	--	U

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived
N/a = Not applicable

June 21, 2011

Bonaventure Akinlosotu, PM Team 10
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Document Processing Desk
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Subject: Efftix® Topical Solution for Dogs (EPA Reg. No 2382-RIT); Revised Proposed Labeling.

Dear Dr. Akinlosotu,

Virbac Animal Health (Virbac AH, Inc. P. O. Box 162059, Ft. Worth, Texas, Company Number 2382), made the submission mentioned above on April 28, 2011. Although not confirmed in writing, we understand the unofficial PRIA date of this action is November 19, 2011. Please confirm this for us as soon as possible for our records. We see that the submitted studies are in NPIRS, but we also still have not received a confirmatory PR-86-5 compliance statement from the front end.

During the course of the beginning phases of label printing and production, Virbac has located some minor errors and word changes in the original submitted label that it wishes to be refelected on the final stamped label. Therefore please find five copies of proposed labeling that we request be utilized in the label review process of this submission. For security, please shred for us the original labels carrying the date of April 28, 2011.

Sincerely,

Craig Parks, MS, DVM
Vice President, Research & Development
Virbac Animal Health, Inc.

Virbac's Master Label

Date 21JUN11 **Version** US-9 **EPA Reg. No.** 2382-RIT
Fipronil+Permethrin Topical Solution for Dogs

Optional text appears in brackets.

EFFITIX™ TOPICAL SOLUTION FOR DOGS

Alternate brand names:

(EFFIX™ TOPICAL SOLUTION FOR DOGS)

(EFFICANIX™ TOPICAL SOLUTION FOR DOGS)

(EFFIPROTIX™ TOPICAL SOLUTION FOR DOGS)

FOR USE ONLY ON DOGS AND PUPPIES 8 WEEKS OLD OR OLDER (WEIGHING UP TO 22.9 LBS, WEIGHING 23 TO 44.9 LBS, WEIGHING 45 TO 88.9 LBS, WEIGHING 89 TO 132 LBS)

ACTIVE INGREDIENTS:	
Fipronil	6.01%
Permethrin*	44.88%
OTHER INGREDIENTS:	49.11%
TOTAL:	100.00%

* cis/trans ratio: maximum 55% (±) cis and minimum 45% (±) trans

KEEP OUT OF REACH OF CHILDREN

CAUTION

READ ENTIRE LABEL BEFORE EACH USE

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

HAZARDS TO HUMANS

Harmful if swallowed. Causes eye irritation. Avoid contact with skin, eyes, or clothing. Wash hands thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco, or using the toilet.

HAZARDS TO DOMESTIC ANIMALS

For external use on dogs ONLY.

DO NOT USE ON CATS – IF INGESTED BY CAT THAT ACTIVELY GROOMS A RECENTLY TREATED DOG, THIS PRODUCT MAY HAVE SERIOUS HARMFUL EFFECTS. IF THIS OCCURS, CONTACT YOUR VETERINARIAN IMMEDIATELY.

Do not use on puppies under 8 weeks of age. Individual sensitivities, while rare, may occur after using ANY pesticide product. Dogs may experience some temporary irritation at the site of product application. If signs of sensitivity occur, bathe your pet with mild soap or shampoo and rinse with large amounts of water. If signs of sensitivity occur and persist, contact a veterinarian immediately. If your dog has an unusual reaction to the initial application, consult a veterinarian before repeating application. Certain medications can interact with pesticides. Consult a veterinarian before using on medicated, debilitated, aged, pregnant or nursing dogs, or animals known to be sensitive to pesticide products.

FIRST AID	
IF SWALLOWED:	• Call a poison control center or doctor immediately for treatment advice. • Have person sip a glass of water if able to swallow. • Do not induce vomiting unless told to do so by a poison control center or doctor. • Do not give anything to an unconscious person.
IF IN EYES:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
IF ON SKIN OR CLOTHING :	• Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes. • Call a poison control center or doctor for treatment advice.
Have product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact the Hotline number 1-800-338-3659 for human or veterinary health concerns, emergency medical treatment Information or pesticide Incidents.	

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in any manner inconsistent with its labelling. Do not allow children to apply product. TO PREVENT HARM TO YOU AND YOUR DOG, READ ENTIRE LABEL AND DIRECTIONS BEFORE EACH USE. FOLLOW ALL DIRECTIONS AND PRECAUTIONARY STATEMENTS CAREFULLY. FOR EXTERNAL USE ON DOGS ONLY. DO NOT USE ON CATS OR RABBITS. DO NOT USE ON OTHER ANIMALS.
DO NOT USE ON CATS.
FOR EXTERNAL USE ON DOGS ONLY. Do not use on puppies under 8 weeks of age. Do not split tubes between dogs. Do not use multiple tubes on one dog. Weigh your dog to be sure you are applying the right dose formulated for the weight of your dog. Overdosing your dog can result in serious illness. Do not bathe your dog within the first 24 hours after the product has been applied. If your dog is exhibiting signs of and/or is being treated for skin problems, talk to your veterinarian before applying any topical flea and tick control product.

Do not apply more often than once a (per) month (every 30 days).

For use in DOGS and PUPPIES (8 weeks old or older). To repel and kill fleas, ticks, and mosquitoes; to kill lice and mites; to repel and prevent blood feeding by sandflies and biting flies. Apply monthly according to directions.

APPLICATION DIRECTIONS

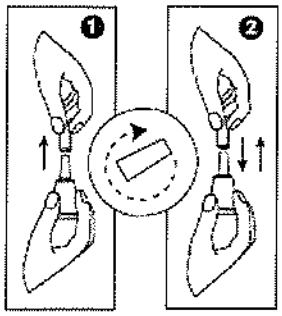
1. Remove one applicator from packaging.
   Hold applicator upright and remove cap.
2. Invert cap and place other end back onto applicator tip.
   Push cap down to break seal.
   Remove cap prior to treatment application.
3. Part dog's hair until skin is visible.
   Place applicator tip directly against exposed skin.

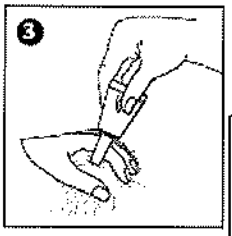
3a. **For small dogs and puppies 8 weeks old or older and up to 22.9 lbs-** Deposit entire contents by squeezing the entire applicator contents onto dog's skin, at a single site, between the shoulder blades as shown in diagram 3a.

3b. **For medium dogs 23-44.9 lbs or large dogs 45-88.9 lbs-** Apply the product evenly to three spots on the dog's back starting between the shoulder blades and continuing on to the second and third spots as shown in diagram 3b, squeezing the applicator until empty.

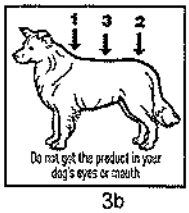
3c. **For extra large dogs 89-132 lbs-** Apply the product evenly to four spots on the dog's back, starting between the shoulder blades and continuing on to the second, third and fourth spots as shown in diagram 3c, squeezing the applicator until empty.

Ensure that EFFITIX™ Topical Solution for Dogs is not applied superficially on dog's hair.





3a



3b

3c

FREQUENCY OF APPLICATION
Research has shown that flea, tick, (sucking, biting and chewing) lice and mite infestations, can be completely controlled with monthly applications of EFFITIX™ Topical Solution for Dogs. Biting flies and mosquitoes are (also) repelled by EFFITIX™ Topical Solution for Dogs.

Fleas: EFFITIX™ Topical Solution for Dogs can start killing adult fleas within 6 hours and lasts for up to three months. Apply monthly if your dog has fleas that may cause flea allergy dermatitis (FAD), or if re-infestation is likely.
Ticks: EFFITIX™ Topical Solution for Dogs can kill ticks for at least a month. Apply monthly where tick control is consistently needed.
Lice: EFFITIX™ Topical Solution for Dogs can kill sucking, biting and chewing lice for a month or longer. Apply monthly where lice control is consistently needed.
Mites: When applied monthly, EFFITIX™ Topical Solution for Dogs kills mites.
Biting flies and Mosquitoes: When applied monthly, EFFITIX™ Topical Solution for Dogs (prevents blood feeding by) (and) (kills) (and) (repels) biting flies and mosquitoes for up to 4 weeks (a (one] month). Kills mosquitoes for up to four weeks (a [one] month).

Notes: Wait at least 30 days before re-application of EFFITIX™ Topical Solution for Dogs. Avoid contact with treated area until dry.

STORAGE AND DISPOSAL

Do not contaminate water, food, or feed by storage and disposal.

STORAGE: Store unused product in original container only, out of reach of children and animals.

PESTICIDE /CONTAINER DISPDSAL: If empty: Nonrefillable. Do not reuse or refill this container. Offer for recycling, if available. **If partially filled:** Call your local solid waste agency for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND DISCLAIMER

VIRBAC warrants this product only if it is used, stored and handled in accordance with the label instructions. The buyers and users are solely responsible for all risks of use and handling of this product when such use and handling are contrary to or differ from the label instructions. To the extent permitted by applicable law, any damages arising from a breach of this warranty shall be limited to direct damages only and shall not include any type of consequential damages.

How supplied: For easy and convenient application, EFFITIX™ Topical Solution for Dogs is available in sizes for small dogs and puppies 8 weeks old or older and up to 22.9 lbs (0.034 fl oz)/(1.0 mL), medium dogs 23-44.9 lbs (0.068 fl oz)/(2.0 mL), large dogs 45-88.9 lbs (0. t35 fl oz)/(4.0 mL), and extra large dogs 89-132 lbs (0.203 fl oz)/(6.0 mL).
Net Contents: 1 (3, 6 or 36) single-dose applicator(s) per package containing 1mL (2mL, 4mL or 6mL)/ 0.034 fl oz (0.068 fl oz, 0.135 fl oz, 0.203 fl oz) (of solution).

(Detachable) calendar (monthly application) reminder stickers (with illustration of dog or puppy)

EPA Reg. No. 2382-RIT
EPA Est. No. 2382-FRA-1

VIRBAC AH, INC.
PO BOX 162059
FORT WORTH TX 76161
1-800-338-3659

Made in France
EFFITIX™ is a trademark of Virbac S.A.
Questions or comments?
Call: 1-800-338-3659

{Text for Front Panel, Back Panel, Inside Flap and Side Panel}

See package insert(s) for directions for use and frequency of application
See package insert for directions for use and storage and disposal
See package insert for frequency of application and storage and disposal
Open resealable label for directions for use
Open resealable label for directions for use and storage and disposal
See back panel for additional precautionary statements
See package insert(s) for frequency of application
See enclosed insert(s) for directions for use and storage and disposal
See enclosed insert(s) for directions for use
Lift here to open (LIFT HERE TO OPEN)
For Use on Dogs ONLY
Use ONLY on dogs
See inside flap for directions for use

{Text for Foil of Blister package}

Virbac
EFFITIX™ Topical Solution For Dogs

Only for use on dogs up to 22.9 lbs (23-44.9 lbs, 45-88.9 lbs, 89-132 lbs)/0.034 fl oz (0.068 fl oz, 0.135 fl oz, 0.203 fl oz) (1.0 mL, 2.0 mL, 4.0 mL, 6.0mL)
Contains fipronil (6.01%) and permethrin (44.88%)
KEEP OUT OF REACH OF CHILDREN
CAUTION
See full label for additional directions
EPA Reg. No. 2382-XXX
DO NOT USE ON CATS
CAT PROHIBITION ICON

{Text for Applicator Tube}

Virbac
EFFITIX™
Topical Solution For Dogs
Only for use on dogs
up to 22.9 lbs (23-44.9 lbs, 45-88.9 lbs, 89-132 lbs)
0.034 fl oz (0.068 fl oz, 0.135 fl oz, 0.203 fl oz) [/ t.0 mL (2.0 mL, 4.0 mL, 6.0mL)[
Contains fipronil (6.01%)
and permethrin (44.88%)
KEEP OUT OF REACH OF CHILDREN
CAUTION
See full label for additional directions
DO NOT USE ON CATS
EPA Reg. No. 2382-XXX
CAT PROHIBITION ICON

- Illustration of flea life cycle
- Illustration of tick life cycle
- Illustration of mosquito life cycle
- Illustration of mite life cycle
- Illustration of louse life cycle
- Illustration of flea
- Illustration of tick
- Illustration of mosquito
- Illustration of mite
- Illustration of louse
- Picture or illustration of a dog (or puppy)
- Picture or illustration of the Virbac logo
- Picture or illustration of the primary package (applicator tubes)

MARKETING CLAIMS

[Multiple infestations]

- For convenient, quick-acting, long-lasting, effective control of fleas, ticks, mosquitoes, lice and mites.
- (When) Applied topically on a monthly basis, EFFITIX™ Topical Solution for Dogs repels and kills fleas, ticks and mosquitoes, kills (biting, chewing and sucking) lice and mites, and repels and inhibits blood feeding by biting flies and mosquitoes.
- (When) Applied topically on a monthly basis, EFFITIX™ Topical Solution for Dogs repels and kills fleas, ticks and mosquitoes, kills (biting, chewing and sucking) lice and mites, and repels and inhibits blood feeding by biting flies, sandflies and mosquitoes.
- For easy and convenient application, EEFITIX™ Topical Solution for Dogs is available in sizes for small dogs and puppies 8 weeks old or older and up to 22.9 lbs (0.034 fl oz)(1.0 mL), medium dogs 23-44.9 lbs (0.068 fl oz) (2.0mL), large dogs 45-88.9 lbs (0.135 fl oz) (4.0 mL), and extra large dogs 89-132 lbs (0.203 fl oz) (6.0 mL).
- EFFITIX™ Topical Solution for Dogs contains the active ingredients fipronil and permethrin, which control infestations caused by fleas, ticks, lice, and mites; repel against biting flies, and repel and kill mosquitoes.
- EFFITIX™ Topical Solution for Dogs contains the active ingredients fipronil and permethrin, which control infestations caused by fleas, ticks, lice, and mites; repel against biting flies, and sandflies, and repel and kill mosquitoes.
- Kills fleas, ticks, lice, mites and mosquitoes, repels biting flies and mosquitoes
- Repels and kills fleas and ticks
- Repels fleas, ticks, biting flies and mosquitoes
- Repels fleas, ticks, biting flies, sandflies and mosquitoes
- Kills, repels and detaches ticks
- Kills lice and mites
- For the control and prevention of flea [and lice] infestations
- Research has shown that flea, tick, (sucking, biting and chewing) lice and mite infestations, can be completely controlled with monthly applications of EFFITIX™ Topical Solution for Dogs. Biting flies and mosquitoes are (also) repelled by EFFITIX™ Topical Solution for Dogs.
- Controls highly [irritating[[annoying] [flea] bites
- Effective monthly application against fleas, ticks and mosquitoes
- Kills fleas, ticks and mosquitoes for one month
- Monthly application is recommended for control and prevention of fleas, ticks and mosquitoes

- Long lasting flea, tick and mosquito control for your pet
- EFFITIX™ Topical Solution for Dogs is indicated for the prevention and control of fleas, ticks, biting flies, mosquitoes, and lice on dogs 8 weeks of age and older
- Helps to relieve your dog's pain (discomfort) by controlling flea, tick, mite and lice infestations
- Kills the vectors that may transmit Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, hepatozoonosis and heartworm disease.
- Kills fleas, ticks, mosquitoes, lice, and mites
- Kills and repels fleas, ticks, and mosquitoes.
- (Also) kills tice and mites.

[Fleas]

- Fleas: EFFITIX™ Topical Solution for Dogs can kill adult fleas in 6 hours for up to three months. Apply monthly if your dog has fleas that may cause flea allergy dermatitis (FAD), or if reinfestation is likely.
- Kills newly emerged adult fleas prior to egg laying
- Kills fleas (within 6 hours) that may transmit bartonellosis, (tularemia) (and tapeworm)
- Kills fleas (within 6 hours) that may transmit diseases, including bartonellosis, (tularemia) (and tapeworm infestations)
- Kills fleas (within 6 hours) that may transmit diseases, including bartonellosis and tularemia
- Rapid kill of fleas is important in the prevention of disease transmission by (these) parasites
- Acts to kill fleas that may transmit disease, such as bartonellosis and tularemia
- Kills fleas that may serve as an intermediate host for tapeworms (*Dipylidium caninum*)
- Kills fleas that may serve as an intermediate host for cysticercoids of tapeworms
- Kills fleas that may serve as hosts for life cycle intermediates of tapeworms
- Kills (adult) fleas (within 6 hours) that may cause Flea Allergy Dermatitis (FAD) (or) (flea-bite anemia)
- Fleas do not have to bite to die
- EFFITIX™ Topical Solution for Dogs rapidly kills fleas that may cause FAD (Flea Allergy Dermatitis)
- The successive feeding activity of fleas on dogs may elicit a hypersensitivity skin disorder known as Flea Allergy Dermatitis (FAD)
- EFFITIX™ Topical Solution for Dogs kills fleas and may reduce the incidence of Flea Allergy Dermatitis (FAD)
- Effective monthly application against fleas
- Effective monthly control of fleas
- Kills adult fleas for up to one month (4 weeks)
- Kills fleas
- Easy to apply, (effective) control of (for) fleas that lasts up to 1 month (4 weeks)
- EFFITIX™ Topical Solution for Dogs kills fleas on your dog
- Once a month topical flea control for dogs 8 weeks of age or older
- EFFITIX™ Topical Solution for Dogs is indicated for the prevention and control of fleas on dogs 8 weeks of age and older
- One application prevents further flea infestations for up to (4 weeks) (a [one] month)
- Monthly treatment (all year) is recommended for control and prevention of fleas
- Regular (monthly) use breaks the flea life cycle
- Provides ongoing protection against fleas and the diseases they may transmit for one month
- Stops existing flea infestations by rapidly killing adult fleas
- Kills fleas before they lay eggs
- Stops existing flea infestations by killing adult fleas
- Prevents [Stops] re-infestations by killing adult fleas (before they lay eggs)
- Effectively breaks the flea life cycle
- Treatment with EFFITIX™ rapidly kills fleas which may cause flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Controls flea problems
- Provides flea protection
- Use flea [prevention[[protection[year-round
- EFFITIX™ Topical Solution for Dogs controls flea infestation that may lead to painful skin irritation and bacterial infection

[Ticks]

- Ticks: EFFITIX™ Topical Solution for Dogs can kill ticks for at least a [one] month. Apply monthly where tick control is consistently needed.
- Kills and repels all stages of Brown dog ticks, American dog ticks, Lone Star ticks, and Deer ticks (that may transmit Lyme disease, Rocky Mountain Spotted Fever, babesiosis, ehrlichiosis and anaplasmosis)
- Kills ticks including Deer ticks (that may transmit Lyme disease), American dog ticks (that may transmit Rocky Mountain Spotted Fever), Brown dog ticks (that may transmit ehrlichiosis), and Lone Star ticks (that may transmit hepatozoonosis) for up to one month (4 weeks)
- Kills ticks including Deer ticks (that may transmit Lyme disease), American dog ticks (that may transmit Rocky Mountain Spotted Fever), and Brown dog ticks (that may transmit ehrlichiosis) for up to one month (4 weeks).
- Kills Brown dog ticks (*Rhipicephalus* spp), American dog ticks (*Dermacentor variabilis*), Deer ticks (*Ixodes* spp) and Lone Star ticks (*Amblyomma americanum*) for up to one month (4 weeks).
- Kills *Amblyomma americanum* (Lone Star ticks) for 4 weeks (for up to one month).
- Effective monthly application against ticks

[Mosquitoes, sandflies and biting flies]

- Kills mosquitoes
- Kills mosquitoes for up to 28 days (four weeks) (a (one] month)
- Repels and inhibits blood feeding by biting flies and mosquitoes

- Repels and inhibits blood feeding by biting flies, sandflies and mosquitoes
- Biting flies and mosquitoes: When applied monthly, EFFITIX™ Topical Solution for Dogs prevents blood feeding (repels) for up to 4 weeks (a]one] month)
- Biting flies, sandflies and mosquitoes: When applied monthly, EFFITIX™ Topical Solution for Dogs prevents blood feeding (repels) for up to 4 weeks (a [one] month)
- Repels and kills mosquitoes for up to four (4) weeks
- Prevents blood feeding by mosquitoes
- Repels and prevents blood-feeding by biting flies
- Repels and prevents blood-feeding by sandflies
- Repels and kills mosquitoes often before they have a chance to take a blood meal
- [(Prevents blood-feeding by) (Kills and repels)] mosquitoes
- Repels biting flies
- Repels sandflies
- Repels and inhibits blood-feeding by biting flies
- Repels and inhibits blood-feeding by sandflies
- Repels [(annoying)(bothersome)(nuisance)] biting flies
- Inhibits [(annoying)(bothersome)(nuisance)] biting flies
- Repels [(annoying)(bothersome)(nuisance)] sandflies
- Inhibits [(annoying)(bothersome)(nuisance)] sandflies
- [(Prevents)(inhibits)] blood-feeding by biting flies
- [(Prevents)(inhibits)] blood-feeding by sandflies
- Kills mosquitoes that may carry heartworm disease
- Repels and kills mosquitos (*Culex spp, Ochlerotatus spp, Aedes spp*) which may vector heartworm (*Dirofilaria immitis*) for one month

[Lice and Mites]

- Lice: EFFITIX™ Topical Solution for Dogs can kill sucking, biting and chewing lice for a [one] month or longer. Apply monthly where lice control is consistently needed.
- Mites: When applied monthly, EFFITIX™ Topical Solution for Dogs kills mites.
- Mites (*Cheyletiella yasguri*): When applied monthly, EFFITIX™ Topical Solution for Dogs kills *Cheyletiella yasguri* mites.
- When applied monthly, EFFITIX™ Topical Solution for Dogs aids in the control of sarcoptic mange (mite), and *Cheyletiella yasguri* mite infestations
- Kills mites (that may cause sarcoptic mange)
- Aids in (the) control of sarcoptic mange mite infestation
- Kills chewing, biting and sucking tice
- Controls existing chewing/biting/sucking (chewing, biting and sucking) lice infestations
- Kills [(biting) (chewing)] lice
- For control and prevention of](biting) (chewing)] lice (infestations)
- Stops existing ((biting) (chewing) (sucking)] lice infestations
- Prevents and controls](biting) (chewing)(sucking)[lice (infestations)
- Provides effective control of](biting) (chewing) (sucking)] lice (infestations)
- Kills](biting) (chewing)(sucking)] lice and prevents further infestations
- For control and prevention of (infestations with) [(biting) (chewing) (sucking)] lice

[Others]

- 1 (3, 6, 36) applicator(s) (tube[s]) 1.0 mL (2.0 mL, 4.0 mL, 6.0 mL)
- 1 (3, 6, 36) applicator(s) (tube[s]) 0.034 fl oz (0.068 fl oz, 0.t35 fl oz, 0.203 fl oz)
- 1 (3, 6, 36) applicator(s) (tube[s]) 0.034 fl oz [1.0 mL] (0.068 fl oz]2.0 mL), 0.135 fl oz [4.0 mL], 0.203 fl oz [6.0 mL])
- 1 (3, 6, 36) applicator(s) (tube]s]) (each) containing 0.034 fl oz [1.0 mL] (0.068 fl oz]2.0 mL), 0.t35 fl oz [4.0 mL[, 0.203 fl oz]6.0 mL])
- t (3, 6, 36) applicator(s) (tube[s])
- 1 (3, 6, 36) monthly dose(s) (application]s])
- 1 (3, 6, 36) applicator(s) (tube]s]) 1 (3, 6, 36) month(ly) dose(s) (apptication(s)
- DO NOT USE ON CATS
- (For dogs and puppies) 8 weeks (of age) or older
- May be used on puppies from 8 weeks of age
- This product is only for use on dogs up to 22.9 lbs (weighing 23 to 44.9 lbs, weighing 45 to 88.9 lbs, weighing 89 to 132 lbs)
- Up to 22.9 lbs (weighing 23 to 44.9 lbs, weighing 45 to 88.9 lbs, weighing 89 to t32 lbs)
- Easy and convenient application (applications)
- Remains effective for a (one) month (4 weeks)
- Stops existing infestations and prevents establishment of new infestations
- Reinfestation of fleas, ticks and mosquitoes, (biting, chewing and sucking) lice and mites, and biting flies is prevented for a (one) month or longer
- Convenient topical treatment for dogs
- Quick onset of activity
- Persistent efficacy through 30 days
- Prevents (re-)infestation for one month
- Once monthly application
- Quick drying, non-greasy
- (Convenient) (to use) Easy (to apply) spot-on (topical) application
- Fragrance (odor) free

- No noticeable odors
- Single application lasts 4 weeks (one month) (30 days)
- Easy to use applicator makes treatment simple (trouble free, smooth) and comfortable for your pet
- Convenient, easy to apply topical solution
- Convenient, easy to apply and fragrance free topical solution
- Starts working by (on) contact
- (In) child-resistant packaging
- Convenient (to use), easy to apply (topical solution)
- EFFITIX™ Topical Solution for Dogs remains effective after bathing, shampooing, water immersion, or sunlight exposure.
- Waterproof (remains effective after bathing and swimming) for up to four weeks (a month) (one month)
- Remains effective after exposure to sunlight
- Remains effective even after bathing, water immersion, or exposure to rain or sunlight
- Remains effective even after bathing (and swimming)
- Remains effective after exposure to rain and/or sunlight
- Still works after bathing, swimming or exposure to sunlight
- Maintains residual efficacy after bathing and swimming
- Remains effective after bathing (and swimming) [(for a month) (for one month) (for up to four weeks)]
- For dogs that enjoy the outdoors
- For indoor and outdoor dogs
- Convenient topical treatment for dogs who enjoy the outdoors
- Formulated for dogs that love the outdoors
- For dogs that enjoy the outdoors
- Available from licensed veterinarians
- Sold by veterinarians
- Veterinarian recommended

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

CHILD-RESISTANT PACKAGING REVIEW
Technical Review Branch

IN 06/16/2011 OUT 08/05/2011

RD, TRB, Reviewed by Rosalind L. Gross 08/05/2011

EPA Reg. No. or File Symbol 2382-RIT

DP Barcode DP390819

Decision # 448350
EPA Petition or EUP No. _____

Date Division Received 04/28/2011

Type Product(s) Insecticide (flea product)

Data Accession No(s). MRID numbers 48467130, 48467131, 48467132, 48467133, 48467134, 48467135, 48467136, 48467137, 48467138, 48467139, 48467140, 48467141, 48467142, 48467143, 48467144, 48467145

Product Mgr./Chemical Review Mgr/Contact Person RM 10 Bonaventure Akinlosotu
Division RD

Product Name(s) Effitix Topical Solution for Dogs

Company Name(s) Virbac AH, Inc.

Submission Purpose Review of CRP studies to determine if they are adequate to support CRP certification for this product in 4 fill levels in 3 tube sizes in 4 retail sizes (1, 3, 6, 36 tubes/retail package)

Active Ingredient(s), PC code, & % Fipronil 6.01%
Permethrin 44.88%

Summary of Findings

In conclusion all the requirements for CRP have been met for EPA Reg. No. 2382-RIT as a 1, 3, 6, and 36 tube package with a 1ml fill level in a 1ml tube, a 2ml fill level in a 3ml tube, a 4ml fill level in a 6ml tube, and a 6ml fill level in a 6ml tube. The directions on opening the package given to consumers must be identical to those given to the seniors during testing for the tubes (see package section for exact language). All 4 fill levels in 3 tube sizes (1ml tube with 1 ml placebo, 3ml tube with 2ml placebo, 6ml tube with 4ml placebo, 6ml tube with 6ml placebo) in 4 retail sizes (1, 3, 6, 36 tubes/retail package) meet the CRE requirements in 16 CFR 1700.20 and SAUE effectiveness specifications in 16 CFR 1700.15(b)(2)(i) when tested in accordance with 16 CFR 1700.20. **For the details of each study refer to the attached summary chart (selfcertreviewsummarycht2382-187.doc).**

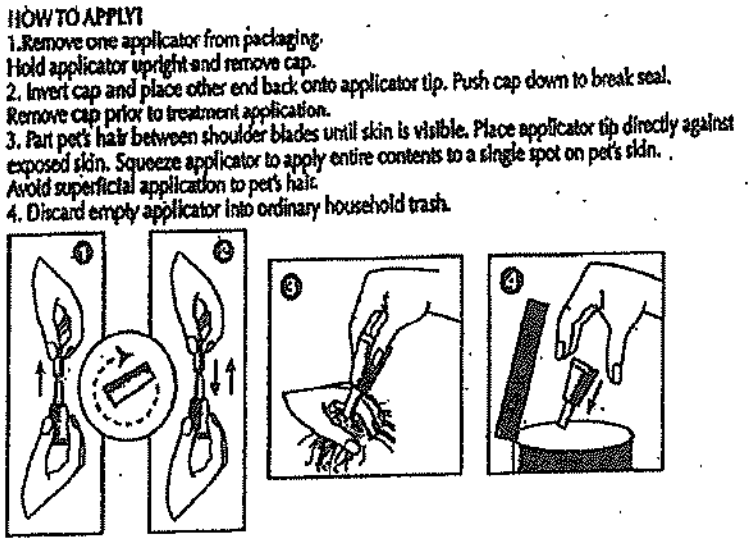
The **CRP certification submitted April 28, 2011** for EPA Registration No. 2382-RIT is acceptable. **The April 13, 2011 master label (pin punched April 28, 2011)** for EPA Registration No. 2382-RIT has the CRP directions used in SAUE testing on page 2. **Note** the package insert and all locations where directions for use refer to the CRP being opened **must have the same directions as used in the SAUE testing as per MRID 48467130 1710-072 as discussed in the package section.** After the text for applicator tube on page 4 a **"picture or illustration of the primary package (applicator tubes)"** is mentioned. This is not allowed unless the tube picture is part of artwork in the directions as used in the SAUE testing (MRID 48467130 1710-072 in the package section). **The CRP directions in all locations on the final stamped label must be identical to those used in SAUE testing.**

Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the child resistance of the package involved.

Package

The package is a white plastic tube with a white closure containing a pin. The closure (19.0 mm x 8.25 mm) is a rexam polyoxymethylene closure with a pin and a rexam PP liner. The tube has a neck (cannula), which is sealed. The closure fits onto the tube neck. The pin is recessed from the top of the closure. The closure pulls off the tube and is inverted and pushed down for the pin to puncture the tube neck. The closure is then removed to release the product. The tube is the child-resistant feature. The tube comes in 3 different sizes with 4 fill levels of water as a placebo (1ml tube with 1 ml placebo, 3ml tube with 2ml placebo, 6ml tube with 4ml placebo, 6ml tube with 6ml placebo). The tube comes in packages of 1 tube, 3 tubes, 6 tubes, or 36 tubes.

The writing on the tube is in black ink. The tube has no instructions for opening the package. The instruction given to Seniors during CRP testing were in the addendum of the Senior Adult Use Effectiveness (SAUE) studies directing the Seniors to "Please open one tube according to directions 1 & 2 on this paper....." and the Seniors were provided the package insert and directed to the following instructions (from MRID48467130, 1710-072):



Toxicity

The toxicity of the product is based only on the toxicity of Fipronil. The toxic or harmful amount of Fipronil for an 11.4 kg child is 2.5mg/kg times 11.4kg, which equals 28.5mg. Access to a toxic or harmful amt = **28.5mg** = 28.5mg divided by [1114mg/ml x 0.0601 Fipronil] = **0.43 ml for** EPA REG # 2382-RIT Effitix Topical Solution for Dogs.

Failure

For the purposes of CRP testing **a child failure** is access to 1 unit. Access to 1 unit is more than 28.5mg of Fipronil for all sizes greater than 0.43 ml. A **unit failure** is opening the tube or any partial or complete access to the placebo (water).
A Senior Adult Use Effectiveness failure is failure to access the tube contents in the prescribed test time of 5 minutes for the first package or 1 minute for the second package, not accessing the tube contents in the correct manner in the prescribed test time of 5 minutes for the first package or 1 minute for the second package.

Analysis of Data and Conclusion

The **CRP certification submitted April 28, 2011** for EPA Registration No. 2382-RIT is acceptable. **The April 13, 2011 master label (pin punched April 28, 2011)** for EPA Registration No. 2382-RIT has the CRP directions used in SAUE testing

on page 2. **Note** the package insert and all locations where directions for use refer to the CRP being opened **must have the same directions as used in the SAUE testing as per MRID 48467130 1710-072 as discussed in the package section.** After the text for applicator tube on **page 4 a "picture or illustration of the primary package (applicator tubes)"** is mentioned. This **is not allowed** unless the tube picture is part of artwork in the directions as used in the SAUE testing (MRID 48467130 1710-072 in the package section). **The CRP directions in all locations on the final stamped label must be identical to those used in SAUE testing.**

The CRP written reports included summaries of the test data. A computer analysis and complete review of the 16 Child-Resistant Effectiveness (CRE) and 16 SAUE studies were not done. We used the summaries of the test data in the written reports, the April 28, 2011 CRP certification, and the April 13, 2011 master label (pin punched April 28, 2011) for EPA Registration No. 2382-RIT to evaluate the 4 fill levels in 3 tube sizes in 4 retail sizes. The results of these studies indicate that all 4 fill levels in 3 tube sizes (1ml tube with 1 ml placebo, 3ml tube with 2ml placebo, 6ml tube with 4ml placebo, 6ml tube with 6ml placebo) in 4 retail sizes (1, 3, 6, 36 tubes/retail package) meet the CRE requirements in 16 CFR 1700.20 and SAUE effectiveness specifications in 16 CFR 1700.15(b)(2)(i) when tested in accordance with 16 CFR 1700.20. **For the details of each study refer to the attached summary chart (selfcertreviewsummarycht2382-187.doc).**

In conclusion all the requirements for CRP have been met for EPA Reg. No. 2382-RIT as a 1, 3, 6, and 36 tube package with a 1ml fill level in a 1ml tube, a 2ml fill level in a 3ml tube, a 4ml fill level in a 6ml tube, and a 6ml fill level in a 6ml tube. The directions on opening the package given to consumers must be identical to those given to the seniors during testing for the tubes (see package section for exact language).

Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the child resistance of the package involved.

August 3, 2011

CRPdatasummarycht
EPA REG # 2382-RIT Effitix Topical Solution for Dogs

207

Company Name Virbac AH, Inc.

Chemical - Fipronil 6.01%
Permethrin 44.88%

A **Senior Adult Use Effectiveness failure** is failure to access the tube contents in the prescribed test time of 5 minutes for the first package or 1 minute for the second package, not accessing the tube contents in the correct manner in the prescribed test time of 5 minutes for the first package or 1 minute for the second package.
A **child failure** is access to 1 unit. Access to 1 unit is more than 28.5mg of Fipronil for all sizes greater than 0.43 ml.
A **unit failure** is opening the tube or any partial or complete access to the placebo (water).

Access to a toxic or harmful amt = **28.5mg** = 28.5mg divided by [1114mg/ml x 0.0601 Fipronil] = **0.426ml = 0.43ml for Fipronil & Permethrin Dog Product** EPA REG # 2382-RIT

% AI - Fipronil 6.01%
Permethrin 44.88%

Note:

1. **The tube is the child-resistant feature.**
2. **The tubes are filled in ml.**

EPA REG #	MRID	amt placebo / prod Fl. Oz. (29.6ml =1 fl.oz)	amt placebo / prod ml (ml = 0.0338 fl. oz.)	PKG Description Include ml per Pkg # unit/pkg, child fail = # units, color, tox/harm = # units	# Pkges Child Get at Begin Test	CRE # child test	SAUE	Conclusion
2382-RIT	48467130 1710-072	0.034	1ml	a 1 ml size tube with1ml (placebo/product)	1 tube	50 child test - 1 child failure pass sequential test 16 CFR 1700.20	100% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467134 1710-076	0.068	2ml	a 3 ml size tube with 2ml (placebo/product)	1 tube	50 child test - 5 child failures pass sequential test 16 CFR 1700.20	100% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467138 1710-080	0.135	4ml	a 6 ml size tube with 4ml (placebo/product)	1 tube	50 child test - 1 child failure pass sequential test 16 CFR 1700.20	100% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes

EPA REG #	MRID	amt placebo / prod Fl. Oz. (29.6ml =1 fl.oz)	amt placebo / prod ml (ml = 0.0338 fl. oz.)	PKG Description Include ml per Pkg # unit/pkg, child fail = # units, color, tox/harm = # units	# Pkges Child Get at Begin Test	CRE # child test	SAUE	Conclusion
2382-RIT	48467142 1710-084	0.203	6ml	a 6 ml size tube with 6ml (placebo/product)	1 tube	50 child test - 1 child failure pass sequential test 16 CFR 1700.20	100% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467131 1710-073	0.034	1ml	a 1 ml size tube with1ml (placebo/product)	3 tube	50 child test - no child failures pass sequential test 16 CFR 1700.20	98% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467135 1710-077	0.068	2ml	a 3 ml size tube with 2ml (placebo/product)	3 tube	100 child test - 9 child failures pass sequential test 16 CFR 1700.20	98% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes

EPA REG #	MRID	amt placebo / prod Fl. Oz. (29.6ml =1 fl.oz)	amt placebo / prod ml (ml = 0.0338 fl. oz.)	PKG Description Include ml per Pkg # unit/pkg, child fail = # units, color, tox/harm = # units	# Pkges Child Get at Begin Test	CRE # child test	SAUE	Conclusion
2382-RIT	48467139 1710-081	0.135	4ml	a 6 ml size tube with 4ml (placebo/product)	3 tube	50 child test - 4 child failures pass sequential test 16 CFR 1700.20	100% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467143 1710-085	0.203	6ml	a 6 ml size tube with 6ml (placebo/product)	3 tube	50 child test - 1 child failure pass sequential test 16 CFR 1700.20	98% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467132 1710-074	0.034	1ml	a 1 ml size tube with1ml (placebo/product)	6 tubes	50 child test - 1 child failure pass sequential test 16 CFR 1700.20	95% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes

EPA REG #	MRID	amt placebo / prod Fl. Oz. (29.6ml =1 fl.oz)	amt placebo / prod ml (ml = 0.0338 fl. oz.)	PKG Description Include ml per Pkg # unit/pkg, child fail = # units, color, tox/harm = # units	# Pkges Child Get at Begin Test	CRE # child test	SAUE	Conclusion
2382-RIT	48467136 1710-078	0.068	2ml	a 3 ml size tube with 2ml (placebo/product)	6 tubes	50 child test - 4 child failures pass sequential test 16 CFR 1700.20	99% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467140 1710-082	0.135	4ml	a 6 ml size tube with 4ml (placebo/product)	6 tubes	50 child test - 1 child failure pass sequential test 16 CFR 1700.20	99% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467144 1710-086	0.203	6ml	a 6 ml size tube with 6ml (placebo/product)	6 tubes	50 child test - no child failures pass sequential test 16 CFR 1700.20	98% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. **Note p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes

EPA REG #	MRID	amt placebo / prod Fl. Oz. (29.6ml =1 fl.oz)	amt placebo / prod ml (ml = 0.0338 fl. oz.)	PKG Description Include ml per Pkg # unit/pkg, child fail = # units, color, tox/harm = # units	# Pkges Child Get at Begin Test	CRE # child test	SAUE	Conclusion
2382-RIT	48467133 1710-075	0.034	1ml	a 1 ml size tube with1ml (placebo/product)	36 tubes	50 child test - 1 child failure pass sequential test 16 CFR 1700.20	98% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. Note **p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467137 1710-079	0.068	2ml	a 3 ml size tube with 2ml (placebo/product)	36 tubes	50 child test - 4 child failures pass sequential test 16 CFR 1700.20	99% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. Note **p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes
2382-RIT	48467141 1710-083	0.135	4ml	a 6 ml size tube with 4ml (placebo/product)	36 tubes	50 child test - 2 child failures pass sequential test 16 CFR 1700.20	100% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. Note **p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes

EPA REG #	MRID	amt placebo / prod Fl. Oz. (29.6ml =1 fl.oz)	amt placebo / prod ml (ml = 0.0338 fl. oz.)	PKG Description Include ml per Pkg # unit/pkg, child fail = # units, color, tox/harm = # units	# Pkges Child Get at Begin Test	CRE # child test	SAUE	Conclusion
2382-RIT	48467145 1710-087	0.203	6ml	a 6 ml size tube with 6ml (placebo/product)	36 tubes	50 child test - no child failures pass sequential test 16 CFR 1700.20	100% SAUE	Meet 16 CFR 1700.20 CRE Criteria - yes Meet 16 CFR 1700.20 SAUE Criteria - yes 4/13/2011 master label (pin punched 4/28/2011) on p 2 matches SAUE test pkg instruct. Note **p4 after tube text not allowed picture of applicator tube as not part of SAUE test pkg instruct. Label is limited to SAUE test pkg instruct.** CRP Cert date & status - 4/28/2011 acceptable all requirements for CRP per 16 CFR 1700.20 -yes

*replaces initial ltr.

485107-00

Virbac
ANIMAL HEALTH

April ~~28, 2011~~ 6/16/2011

Richard Gebken, PM 10
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Document Processing Desk (REGFEE)
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Subject: EFFITIX™ Topical Solution for Dogs (EPA File Symbol 2382-TBA); New Product Application.

Dear Mr. Gebken,

Virbac Animal Health (Virbac AH, Inc. P. O. Box 162059, Ft. Worth, TX 76137, (Company Number 2382) is hereby submitting an application to register the spot-on pesticide product EFFITIX™ Topical Solution for Dogs.

This product contains the active ingredients fipronil at 6.01% w/w, and permethrin at 44.88% w/w and is intended to control fleas, ticks, mosquitoes, and other pests in dogs only.

Permethrin itself is registered alone and in combination with other active ingredients in numerous end use products for spot-on insecticide use in dogs. There are also permethrin alone spot on products registered for dogs that contain up to 65% active ingredient w/w.

As indicated on Form 8570-34, Virbac is using the selective method to address applicable data requirements for this application pursuant to 40 CFR 152.90. Pursuant to 40 CFR 152.93, Virbac has issued Offer to Pay letters to the submitters of data cited in Virbac's application that were originally submitted within the past 15 years.

Below is a list of the components included with this application:

1. Cover Letter;
2. Transmittal Document;
3. Application for Pesticide Form 8570-1 for Effitix™ Topical Solution For Dogs;
4. Confidential Statement of Formula for Effitix™ Topical Solution for Dogs - 2 Copies;
5. Data Matrix Form 8570-4 for Effitix™ Topical Solution for Dogs;
6. Certification of Data Citation Form 8570-34 For Effitix™ Topical Solution For Dogs;
7. Proposed Label - Use Directions for Effitix™ Topical Solution for Dogs - 5 copies;
8. 3 copies of bound PR 86-5 compliant study reports supporting registration;
9. Waiver Request for Acute Inhalation Study (attached to Cover Letter);
10. Letter of Self-certification of Child-Resistant Packaging.
11. Data Matrix listing submitted and cited data in support of the unregistered

3200 Meacham Blvd. • Fort Worth, TX 76137 Telephone: (817) 831-5030 • (800) 338-3659 •
Fax (817) 831-8327

Fipronil TGAI source previously approved for use in manufacturing the registered products 2382-185 and 2382-186.

12. Copy of PRIA Check for category R-310 ($4807).

Child-Resistant Packaging Testing & Data

EFFITIX™ Topical Solution for Dogs and will be marketed in single dose unit applicators that are designed to be Child Resistant. Included with this submission are reports supporting CRP certification of all proposed presentations of the product applicator that are found on the proposed product label. In addition to the written reports, a CD containing raw data required under PR 97-9 has been included with this application.

PRIA Considerations

After reviewing the Agency's PRIA category interpretations, we believe that the R-310 PRIA category and a 6 month review period is appropriate for this product. Consequently, please find a copy of one previously submitted check in the amount of $4807 to cover the PRIA fee.

Should you have any questions about this application package, please do not hesitate to contact me via telephone at 682-647-3576 or via e-mail at craig.parks@virbacus.com.

Sincerely,

Craig Parks, MS, DVM
Vice President, Research & Development
Virbac Animal Health, Inc.

3200 Meacham Blvd. • Fort Worth, TX 76137 Telephone: (817) 831-5030 • (800) 338-3559 •
Fax (817) 831-8327

Virbac Effitix
4/28/2011

TRANSMITTAL DOCUMENT

NAME AND ADDRESS OF SUBMITTER:

Virbac, Inc. (EPA Company Number 2382)
P.O. Box 162059
Fort Worth, TX 76161

REGULATORY ACTION SUPPORTED BY THIS PACKAGE:

This submission is an application to register an end use product named EFFITIX™ Topical Solution for Dogs. EFFITIX™ Topical Solution for Dogs contains the active ingredients Fipronil and Permethrin and is intended to be used as a spot-on product for dogs.

SUBMITTAL DATE:

April 28, 2011

Volume	Study Title	MRID No.
1	Administrative Materials EFFITIX™ Topical Solution for Dogs	
	Group A Product Chemistry	
2	**OPPTS 830.1550, 830.1600, 830. 1620, 830. 1650, 830.1670, 830.1750** Product Specific Chemistry for EFFITIX™ Topical Solution for Dogs	**48467101**
3	**OPPTS 830.1700** Preliminary Analysis (C96541)	**48467102**
4	**OPPTS 830.1800** Enforcement Analytical Method (C96552)	**48467103**
	Group B Product Chemistry	
5	**OPPTS 830.6302, 830.6303, 830.6304** Color, Physical State, Odor (C32753)	**48467104**
6	**OPPTS 830.6314** Oxidation/reduction reactions (C24721)	**48467105**
7	**OPPTS 830.6315** Flash point (C24732)	**48467106**
8	**OPPTS 830.6317** Storage stability (C24697)	**48467107**

Volume	Study Title	MRID No.
9	**OPPTS 830.7000** pH (C24743)	**48487108**
10	**OPPTS 830.7100** Viscosity (C24708)	**48487301**
11	**OPPTS 830.7300** Density/Relative Density (C24710)	**48487110**
	Acute Toxicity	
12	**OPPTS 870. 1100** Acute oral toxicity (C24620)	**48487111**
13	**OPPTS 870.1200** Acute dermal toxicity (C24631)	**48487112**
14	**OPPTS 870.2400** Primary eye irritation (C~~24642~~) 24653	**48487113**
15	**OPPTS 870.2500** Primary dermal irritation (C~~24653~~) 24649	**48487114**
16	**OPPTS 870.2600** Dermal sensitization (C24664)	**48487115**
	Target Animal Safety	
17	**OPPTS 870.7200** Companion animal safety (F 104-05-60012) "A 14 day tolerance study in beagle pups when administered 104.05 (6.7% Fipronil and 50% Permethrin topical solution) topically at 1X and 5X the recommended dose"	**48487302**
18	**OPPTS 870.7200** Companion animal safety (F 104-05-60013) "104.05: Target Animal Safety Study By Dermal Administration to Beagle Dogs"	**48487117**
19	**OPPTS 810.7200** Product Performance (F 104-05-60024) "A 14 day tolerance study in beagle pups when administered 104.05 (6.7% Fipronil and 50% Permethrin topical solution) topically at 1X, 3X and 5X the recommended dose"	**48487118**
20	**OPPTS 870.7200** Companion animal safety Target Animal Safety study summary	**48487119**

Volume	Study Title	MRID No.
21	**OPPTS 870.7200** Companion Animal Safety TSH. Validation of an Immunoassay Method for the Measurement of TSH in Canine Serum.	**48487120**
	Product Performance (Efficacy)	
22	**OPPTS 810.3300** Product Performance (F 104-05-60014) "Efficacy study against fleas (Ctenocephalides Felis) on dogs: Onset of action"	**48510701**
23	**OPPTS 810.3300** Product Performance (F 104-05-60015) "104.05: Efficacy study against Rhipicephalus sanguineus in dogs – duration of action"	**48487122**
24	**OPPTS 810.3300** Product Performance (F 104-05-60016) "104.05: Efficacy study against Dermancentor variabilus in dogs – duration of action"	**48487123**
25	**OPPTS 810.3300** Product Performance (F 104-05-60017) "Efficacy study against the brown dog tick (Rhipicephalus sanguineus) and the cat flea (Ctenocephalides Felis) on dogs : effects of shampooing and periodic water immersions	**48487124**
26	**OPPTS 810.3300** Product Performance (F 104-05-60018) "The duration of efficacy of a single application of 104.05 (6.7% Fipronil and 50% Permethrin topical solution compared to a no treatment control against artificially induced infestation of ticks (amblyoma americanum) on dogs	**48487125**
27	**OPPTS 810.3300** Product Performance (F 104-05-60019) "The duration of efficacy of a single application of 104.05 (6.7% Fipronil and 50% Permethrin topical solution compared to a no treatment control against artificially induced infestation of ticks (ixodes scapularis) on dogs	**48487126**

Volume	Study Title	MRID No.
28	**OPPTS 810.3300** Product Performance (F 104-05-60022) "Determination of efficacy of a combination of Fipronil and Permethrin in topical solution against Mosquitoes (Aedes aegpti) on Dogs"	**48467127**
29	**OPPTS 810.3300** Product Performance (F 104-05-60023) "Repellence study of 104.05 against ticks (Dermancentor variabilus and Rhipicephalus sanguineus) on dogs under laboratory conditions"	**48467128**
30	**OPPTS 810.3300** Product Performance Efficacy study summary	**48467129**
	Child Resistant Packaging	
31	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA (1710-072)	**48467130**
32	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-073)	**48467131**
33	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-074)	**48467132**
34	Evaluation of the 1ml Applicator Tube with 1.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-075)	**48467133**
35	Evaluation of the 3ml Applicator Tube with 2.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA (1710-076)	**48467134**
36	Evaluation of the 3ml Applicator Tube with 2.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-077)	**48467135**
37	Evaluation of the 3ml Applicator Tube with 2.0ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-078)	**48467136**
38	Evaluation of the 3ml Applicator Tube with 2.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-079)	**48467137**
39	Evaluation of the 6ml Applicator Tube with 4.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA (1710-80)	**48467138**

Volume	Study Title	MRID No.
40	Evaluation of the 6ml Applicator Tube with 4.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-81)	48467139
41	Evaluation of the 6ml Applicator Tube with 4.0ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-82)	48467140
42	Evaluation of the 6ml Applicator Tube with 4.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-083)	48467141
43	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA (1710-084)	48467142
44	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-085)	48467143
45	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 6 applicator tubes test as a Poison Prevention Package Virbac SA (1710-086)	48467144
46	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-087)	48467145

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

May 31, 2011

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

NIKITA MAPP
VIRBAC AH, INC.
VIRBAC AH, INC.
13001 ST. CHARLES ROCK ROAD
BRIDGETON, MO 63044-

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your submittal of 19-MAY-11. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your data submittal was found to be partially in compliance with the standards for submission of data contained in PR Notice 86-5, with the exceptions noted below. A copy of your transmittal bibliography is enclosed, annotated with the Master Record lD's (MRIDs) assigned to each document accepted. Please use these numbers in all future references to these documents.

If deficiencies were found which apply to individual accepted studies, they are listed below following the applicable MRID. Any document which has been assigned a MRID has been accepted under PR Notice 86-5. If any comments related to a MRID appear on this report, they are provided for your information and reference when preparing future submissions. Some individual documents were not acceptable, and all copies are being returned to you for correction for the reasons indicated below.

These rejected studies have been assigned separate identification numbers which are annotated on both the enclosed bibliography and the rejected document labels.

The rejected studies and their deficiencies are described below.

Rejected Study [03]:

* You must include one of the two acceptable statements of data confidentiality claims under FIFRA section10(d)(1)(A), (B), or (C) as the second element in each study. The language of two alternative forms of the Statement of Data Confidentiality Claims, shown in Attachment 3 of PR Notice 86-5, cannot be altered. See pages 8 and 13 of the Notice.

* A statement of compliance or non-compliance with the Good Laboratory Practices Standards contained in 40CFR160 is required for all studies (except rangefinding studies and supplements to previously submittedstudies) submitted to EPA. This statement must appearas page 3 of all studies, and must be signed and dated by the study sponsor, the study submitter, and

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

May 12, 2011

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

NIKITA MAPP
VIRBAC AH, INC.
VIRBAC AH, INC.
13001 ST. CHARLES ROCK ROAD
BRIDGETON, MO 63044-

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your submittal of 28-APR-11. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your data submittal was found to be partially in compliance with the standards for submission of data contained in PR Notice 86-5, with the exceptions noted below. A copy of your transmittal bibliography is enclosed, annotated with the Master Record ID's (MRIDs) assigned to each document accepted. Please use these numbers in all future references to these documents.

If deficiencies were found which apply to individual accepted studies, they are listed below following the applicable MRID. Any document which has been assigned a MRID has been accepted under PR Notice 86-5. If any comments related to a MRID appear on this report, they are provided for your information and reference when preparing future submissions. Some individual documents were not acceptable, and all copies are being returned to you for correction for the reasons indicated below.

These rejected studies have been assigned separate identification numbers which are annotated on both the enclosed bibliography and the rejected document labels.

The rejected studies and their deficiencies are described below.

Rejected Study [09]:
* The following page(s) in this study is/are illegibledue to the poor quality of the photocopying: 20, 21, 23, 24.

Rejected Study [16]:
* The following page(s) in this study is/are illegibledue to the poor quality of the photocopying: 59.

Rejected Study [21]:
* Judging from the pagination of the study, page 35 was omitted from the submitted copy.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

April 29, 2011

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OPP Decision Number: D-448350
EPA File Symbol or Registration Number: 2382-RIT
Product Name: EFFITIX TROPICAL SOLUTION FOR DOGS
EPA Receipt Date: 28-Apr-2011
EPA Company Number: 2382
Company Name: VIRBAC AH, INC.

NIKITA MAPP
VIRBAC AH, INC.
13001 ST. CHARLES ROCK ROAD
BRIDGETON, MO 63044-

SUBJECT: Receipt of Registration Application Subject to Registration Service Fee

Dear Registrant:

The Office of Pesticide Programs has received your application and certification of payment. If you submitted data with this application, the results of the PRN-86-5 screen will be communicated separately. During the administrative screen, the Office of Pesticide Programs has determined that this Action is subject to a Pesticide Registration Service Fee as defined in the Pesticide Registration Improvement Act.

The Action has been identified as Action Code: R310

NEW PRODUCT;NON-FAST TRACK (INCLUDES REVIEWS OF PRODUCT CHEMISTRY;ACUTE TOXICITY;PUBLIC HEALTH PEST EFFICACY);

No additional payment is due at this time.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 308-9362.

Sincerely,
Front End Processing Staff
Information Technology & Resources Management Division

TRANSMITTAL DOCUMENT

Submission to US EPA Document Processing Desk

Document Processing Desk
Office of Pesticide Programs
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, Va. 22202-4501

NAME AND ADDRESS OF SUBMITTER:

Virbac AH (EPA Company Number 2382)
P.O. Box 162059
Fort Worth, TX 76161

SUBMITTAL DATE:

April 28, 2011

REGULATORY ACTION SUPPORTED BY THIS SUBMISSION:

Submission of new product application for EFFITIX™ Topical Solution for Dogs.

Confirmation of receipt by US EPA Document Processing Desk

Laurilee Parsons
USEPA Document Processing Desk

04/28/2011
Date/Time

R 310

End Use (EP) or Manufacturing Use (MP) product or Technical Grade of the Active Ingredient (TGAI). Must submit Group A and B product chemistry data for each proposed product unless it's a 100% identical (repack): YES or NO (circle one)

Guideline No.	Group A: Product Chemistry Data Study Title	EP Data Submitted		MP Data Submitted		TGAI	
		Yes	No	Yes	No	Yes	No
830.1550	Product Identity & Composition	✓					
830.1600	Description of materials used to produce the product	✓					
830.1650	Description of formulation process	✓					
830.1670	Discussion on the formation of impurities	✓					
830.1700	Preliminary analysis	✓					
830.1750	Certified limits (158.345)	✓					
830.1800	Enforcement analytical method	✓					

Guideline No.	Group B: Product Chemistry Data Study Title	EP Data Submitted		MP Data Submitted		TGAI	
		Yes	No	Yes	No	Yes	No
830.6302	Color	✓					
830.6303	Physical State	✓					
830.6304	Odor	✓					
830.6313	Stability to normal and elevated temperatures metal and metal ions						
830.6314	Oxidation/Reduction (Chemical incompatibility)	✓					
830.6315	Flammability	✓					
830.6316	Explodability	✓					
830.6317	Storage stability	✓					
830.6319	Miscibility	✓					
830.6320	Corrosion Characteristics	✓					
830.6321	Dielectric Breakdown Voltage	✓					
830.7000	pH	✓					
830.7050	UV/ Visible Absorption						
830.7100	Viscosity	✓					
830.7200	Melting Point						
830.7220	Boiling Point						
830.7300	Density	✓					
830.7370	Dissociation Constant						
830.7550	Partition Coefficient						
830.7840	Water Solubility						
830.7950	Vapor Pressure						

Grayed out = data not required

R 310

New products must either: 1) supply the product specific acute toxicity 6 pack data (listed below), or 2) provide a bridging rationale document. The bridging document directs OPP to use a currently registered set of 6 acute toxicity data and label; instead of submitting product specific data.

Guideline No.	Acute toxicity (6 pack) Study Title	Data submitted		Cited	
		Yes	No	Yes	No
870.1100	Acute Oral (LD50)	✓			
870.1200	Acute Dermal (LD50)	✓			
870.1300	Acute Inhalation (LC50)	✓			
870.2400	Acute Eye Irritation	✓			
870.2500	Acute Dermal Irritation	✓			
870.2600	Dermal Sensitization	✓			

Efficacy – which guideline is used depends on the proposed label use

Guideline No.	Study Title	Data submitted		Cited		Comments
		Yes	No	Yes	No	
810.3100	Soil Treatments for Imported Fire Ants					
810.3200	Livestock, Poultry, Fur and Wool-Bearing Animal Treatments					
810.3300	Treatments to Control Pests of Humans and Pets	✓				
810.3400	Mosquito, Black Fly, and Biting Midge (Sand Fly) Treatments					
810.3500	Premises Treatments					
810.3600	Structural Treatments					
810.3800	Methods for Efficacy Testing of Termite Baits					

Virbac
ANIMAL HEALTH

April 25, 2011

U.S. Bank
Government Lockbox 979074
1005 Convention Plaza
SL-MO-C2-GL
St. Louis, MO 63197

RE: Checks for 2011 PRIA Fees; Virbac AH, Inc. (EPA Co. Number 2382)

Dear Sir or Madam:

Please find enclosed a check numbered **01008652** made out to the Environmental Protection Agency (EPA) in the amount of $4,807.00. This check fulfills the financial obligations in support of an animal health pesticide, to be registered under the company Virbac AH, Inc. (EPA Company Number 2382). Also attached for reference are copies of the EPA Form 8570-1 with information on the registration of the two products with EPA.

Should you have any questions about this application package, please do not hesitate to contact me via telephone at 682-647-3576 or via e-mail at craig.parks@virbacus.com.

Sincerely,

Craig Parks, MS, DVM
Vice President, Research & Development
Virbac Animal Health, Inc.

Virbac AH Inc
Company Number
2382

Virbac ANIMAL HEALTH
P.O. BOX 162059
FT. WORTH, TEXAS 76161
PH. (817) 831-5030

JPMORGAN CHASE BANK, N.A.
DALLAS, TX
88-88/1113

1008652

VOID IF NOT CASHED IN 90 DAYS

PAY Four Thousand Eight Hundred Seven Dollars And Zero Cents

DATE 07-APR-11

CHECK AMOUNT US DOLLARS ******4,807.00

TO THE ORDER OF
USEPA
C/O EXPONENT
ATTN: JIM BARRON
1150 CONNECTICUT AVE. NW STE#1100
WASHINGTON, DC 20036
United States

AUTHORIZED SIGNATURE

AUTHORIZED SIGNATURE

⑈1008652⑈ [redacted]

Commercial/financial information may be entitled to confidential treatment

Virbac
ANIMAL HEALTH

April 28, 2011

Richard Gebken, PM 10
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Document Processing Desk (REGFEE)
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Subject: EFFITIX™ Topical Solution for Dogs (EPA File Symbol 2382-TBA); New Product Application.

Dear Mr. Gebken,

Virbac Animal Health (Virbac AH, Inc. P. O. Box 162059, Ft. Worth, TX 76137, (Company Number 2382) is hereby submitting an application to register the spot-on pesticide product EFFITIX™ Topical Solution for Dogs.

This product contains the active ingredients fipronil at 6.01% w/w, and permethrin at 44.88% w/w and is intended to control fleas, ticks, mosquitoes, and other pests in dogs only.

Permethrin itself is registered alone and in combination with other active ingredients in numerous end use products for spot-on insecticide use in dogs. There are also permethrin alone spot on products registered for dogs that contain up to 65% active ingredient w/w.

As indicated on Form 8570-34, Virbac is using the selective method to address applicable data requirements for this application pursuant to 40 CFR 152.90. Pursuant to 40 CFR 152.93, Virbac has issued Offer to Pay letters to the submitters of data cited in Virbac's application that were originally submitted within the past 15 years.

Below is a list of the components included with this application:

1. Cover Letter;
2. Transmittal Document;
3. Application for Pesticide Form 8570-1 for Effitix™ Topical Solution For Dogs;
4. Confidential Statement of Formula for Effitix™ Topical Solution for Dogs - 2 Copies;
5. Data Matrix Form 8570-4 for Effitix™ Topical Solution for Dogs;
6. Certification of Data Citation Form 8570-34 For Effitix™ Topical Solution For Dogs;
7. Proposed Label - Use Directions for Effitix™ Topical Solution for Dogs - 5 copies;
8. 3 copies of bound PR 86-5 compliant study reports supporting registration;
9. Waiver Request for Acute Inhalation Study (attached to Cover Letter);
10. Letter of Self-certification of Child-Resistant Packaging.
11. Data Matrix listing submitted and cited data in support of the unregistered

3200 Meacham Blvd. • Fort Worth, TX 76137 Telephone: (817) 831-5030 • (800) 338-3659 • Fax (817) 831-8327

Fipronil TGAI source previously approved for use in manufacturing the registered products 2382-185 and 2382-186.

12. Copy of PRIA Check for category R-310 ($4807).

Child-Resistant Packaging Testing & Data

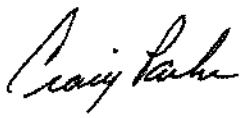
EFFITIX™ Topical Solution for Dogs and will be marketed in single dose unit applicators that are designed to be Child Resistant. Included with this submission are reports supporting CRP certification of all proposed presentations of the product applicator that are found on the proposed product label. In addition to the written reports, a CD containing raw data required under PR 97-9 has been included with this application.

PRIA Considerations

After reviewing the Agency's PRIA category interpretations, we believe that the R-310 PRIA category and a 6 month review period is appropriate for this product. Consequently, please find a copy of one previously submitted check in the amount of $4807 to cover the PRIA fee.

Should you have any questions about this application package, please do not hesitate to contact me via telephone at 682-647-3576 or via e-mail at craig.parks@virbacus.com.

Sincerely,



Craig Parks, MS, DVM
Vice President, Research & Development
Virbac Animal Health, Inc.

3200 Meacham Blvd. • Fort Worth, TX 76137 Telephone: (817) 831-5030 • (800) 338-3559 • Fax (817) 831-8327

TRANSMITTAL DOCUMENT

NAME AND ADDRESS OF SUBMITTER:

Virbac, Inc. (EPA Company Number 2382)
P.O. Box 162059
Fort Worth, TX 76161

REGULATORY ACTION SUPPORTED BY THIS PACKAGE:

This submission is an application to register an end use product named EFFITIX™ Topical Solution for Dogs. EFFITIX™ Topical Solution for Dogs contains the active ingredients Fipronil and Permethrin and is intended to be used as a spot-on product for dogs.

SUBMITTAL DATE:

April 28, 2011

Volume	Study Title	MRID No.
1	Administrative Materials EFFITIX™ Topical Solution for Dogs	
	Group A Product Chemistry	
2	**OPPTS 830.1550, 830.1600, 830. 1620, 830. 1650, 830.1670, 830.1750** Product Specific Chemistry for EFFITIX™ Topical Solution for Dogs	**48467101**
3	**OPPTS 830.1700** Preliminary Analysis (C96541)	**48467102**
4	**OPPTS 830.1800** Enforcement Analytical Method (C96552)	**48467103**
	Group B Product Chemistry	
5	**OPPTS 830.6302, 830.6303, 830.6304** Color, Physical State, Odor (C32753)	**48467104**
6	**OPPTS 830.6314** Oxidation/reduction reactions (C24721)	**48467105**
7	**OPPTS 830.6315** Flash point (C24732)	**48467106**
8	**OPPTS 830.6317** Storage stability (C24697)	**48467107**

Volume	Study Title	MRID No.
9	**OPPTS 830.7000** pH (C24743)	48467108
10	**OPPTS 830.7100** Viscosity (C24708)	48467301
11	**OPPTS 830.7300** Density/Relative Density (C24710)	48467110
	Acute Toxicity	
12	**OPPTS 870. 1100** Acute oral toxicity (C24620)	48467111
13	**OPPTS 870.1200** Acute dermal toxicity (C24631)	48467112
14	**OPPTS 870.2400** Primary eye irritation (C~~24642~~) 24633	48467113
15	**OPPTS 870.2500** Primary dermal irritation (C~~24653~~) 24648	48467114
16	**OPPTS 870.2600** Dermal sensitization (C24664)	48467115
	Target Animal Safety	
17	**OPPTS 870.7200** Companion animal safety (F 104-05-60012) "A 14 day tolerance study in beagle pups when administered 104.05 (6.7% Fipronil and 50% Permethrin topical solution) topically at 1X and 5X the recommended dose"	48487302
18	**OPPTS 870.7200** Companion animal safety (F 104-05-60013) "104.05: Target Animal Safety Study By Dermal Administration to Beagle Dogs"	48467117
19	**OPPTS 810.7200** Product Performance (F 104-05-60024) "A 14 day tolerance study in beagle pups when administered 104.05 (6.7% Fipronil and 50% Permethrin topical solution) topically at 1X, 3X and 5X the recommended dose"	48467118
20	**OPPTS 870.7200** Companion animal safety Target Animal Safety study summary	48467119

Volume	Study Title	MRID No.
21	**OPPTS 870.7200** Companion Animal Safety TSH. Validation of an Immunoassay Method for the Measurement of TSH in Canine Serum.	**48467120**
	Product Performance (Efficacy)	
22	**OPPTS 810.3300** Product Performance (F 104-05-60014) "Efficacy study against fleas (Ctenocephalides Felis) on dogs: Onset of action"	**Reject (03)**
23	**OPPTS 810.3300** Product Performance (F 104-05-60015) "104.05: Efficacy study against Rhipicephalus sanguineus in dogs – duration of action"	**48467122**
24	**OPPTS 810.3300** Product Performance (F 104-05-60016) "104.05: Efficacy study against Dermancentor variabilus in dogs – duration of action"	**48467123**
25	**OPPTS 810.3300** Product Performance (F 104-05-60017) "Efficacy study against the brown dog tick (Rhipicephalus sanguineus) and the cat flea (Ctenocephalides Felis) on dogs : effects of shampooing and periodic water immersions	**48467124**
26	**OPPTS 810.3300** Product Performance (F 104-05-60018) "The duration of efficacy of a single application of 104.05 (6.7% Fipronil and 50% Permethrin topical solution compared to a no treatment control against artificially induced infestation of ticks (amblyoma americanum) on dogs	**48467125**
27	**OPPTS 810.3300** Product Performance (F 104-05-60019) "The duration of efficacy of a single application of 104.05 (6.7% Fipronil and 50% Permethrin topical solution compared to a no treatment control against artificially induced infestation of ticks (ixodes scapularis) on dogs	**48467126**

Volume	Study Title	MRID No.
28	**OPPTS 810.3300** Product Performance (F 104-05-60022) "Determination of efficacy of a combination of Fipronil and Permethrin in topical solution against Mosquitoes (Aedes aegpti) on Dogs"	**48467127**
29	**OPPTS 810.3300** Product Performance (F 104-05-60023) "Repellence study of 104.05 against ticks (Dermancentor variabilus and Rhipicephalus sanguineus) on dogs under laboratory conditions"	**48467128**
30	**OPPTS 810.3300** Product Performance Efficacy study summary	**48467129**
	Child Resistant Packaging	
31	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA (1710-072)	**48467130**
32	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-073)	**48467131**
33	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-074)	**48467132**
34	Evaluation of the 1ml Applicator Tube with 1.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-075)	**48467133**
35	Evaluation of the 3ml Applicator Tube with 2.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA (1710-076)	**48467134**
36	Evaluation of the 3ml Applicator Tube with 2.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-077)	**48467135**
37	Evaluation of the 3ml Applicator Tube with 2.0ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-078)	**48467136**
38	Evaluation of the 3ml Applicator Tube with 2.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-079)	**48467137**
39	Evaluation of the 6ml Applicator Tube with 4.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA (1710-80)	**48467138**

Volume	Study Title	MRID No.
40	Evaluation of the 6ml Applicator Tube with 4.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-81)	48467139
41	Evaluation of the 6ml Applicator Tube with 4.0ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-82)	48467140
42	Evaluation of the 6ml Applicator Tube with 4.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-083)	48467141
43	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA (1710-084)	48467142
44	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-085)	48467143
45	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 6 applicator tubes test as a Poison Prevention Package Virbac SA (1710-086)	48467144
46	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA (1710-087)	48467145

Please read instructions on reverse before completing form

Form Approved, OMB No. 2070-0060, Approval expires 5-31-98

EPA

United States
Environmental Protection Agency
Washington, DC 20460

[X] Registration [ ] Amendment [ ] Other	OPP Identifier Number

Application for Pesticide – Section I

1. Company/Product Number Virbac AH, Inc./ 2382- xxx RIT	2. EPA Product Manager Richard Gebken	3. Proposed Classification [X] None [ ] Restricted
4. Company/Product (Name) EFFITIX™ Topical Solution for Dogs	PM # 10	
5. Name and Address of Applicant (Include ZIP Code) Virbac AH, Inc P.O. Box 162059 Fort Worth, TX 76161 [ ] *Check if this is a new address*	6. Expedited Review. In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to: EPA Reg No. _____ Product Name _____	

Section - II

[ ] Amendment – Explain below

[ ] Resubmission in response to Agency letter dated _____

[ ] Notification – Explain below

[ ] Final printed labels in response to Agency letter dated _____

[ ] "Me Too" Application

[ ] Other – Explain below

Explanation: Use additional page(s) if necessary. (For Section I and Section II.)

Application for registration. PRIA Category R310. Please refer to attached letter.

Section III

1. Material This Product Will be Packaged in:

Child-Resistant Packaging	Unit Packaging		Water Soluble Packaging		2. Type of Container
[x] Yes [ ] No ***Certification must be submitted***	[X] Yes [ ] No If "Yes" Unit Packaging wgt. 0.5	No. per container 1,3,6,36	[ ] Yes [X] No If "Yes" Package wgt	No. per container	[ ] Metal [X] Plastic, PETE [ ] Glass [ ] Paper [ ] Other (Specify) _____

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of label directions
[ ] Label [x] Container	1, 3, 6 ml tubes	[X] On Label [X] On Label accompanying product

6. Manner in Which Label is Affixed to Product: [ ] Lithograph [X] Paper glued [ ] Stenciled [ ] Other _____

Section IV

1. Contact Person (*Complete items directly below for identification of individual to be contacted, if necessary, to process this application.*)

Name	Title	Telephone No. (Include Area Code)
Craig Parks, MS, DVM	Vice President of Research and Development, Virbac AH, Inc.	682-647-3576

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law

2. Signature	3. Title	6. Date Application Received
Craig Parks	Vice President of Research and Development, Virbac AH, Inc.	(Stamped)
4. Typed Name Craig Parks, MS, DVM	5. Date 04/28/2011	

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete. White – EPA File Copy (Original) Yellow – Applicant Copy

Fo pproved. OMB No. 2070-0060. Approval expires 5-31-98

United States
Environmental Protection Agency
Washington, DC 20460

Formulator's Exemption Statement

(40 CFR 152.85)

Applicant's Name and Address	**EPA File Symbol/Registration Number**
Virbac Animal Health P. O. Box 162059 Ft. Worth, TX 76137	2382-NEW
	Product Name EFFITIX™
	Date of Confidential Statement of Formula ***(EPA Form 8570-4)*** March 21, 2011

As an authorized representative of the applicant for registration of the product identified above, I certify that:

(1) This product contains the following active ingredient(s):permethrin

(2) Of these, each active ingredient listed in paragraph (4) is present solely as the result of the use of that active ingredient in the manufacturing, formulation or repackaging another product which contains that active ingredient which is registered under FIFRA Section 3, is purchased by us from another producer, and is labeled for at least each use for which my product is proposed to be labeled.

(3) Indicate by checking (A) or (B) below which paragraph applies:

[X] (A) An accurate Confidential Statement of Formula (*EPA FORM 8570-4*) for the above identified product is attached to this statement. That formula statement indicates, by company name, registration number, and product name, the source of the active ingredient(s) listed in paragraph (1)

OR

[ ] (B) The Confidential Statement of Formula (CSF) (EPA Form 8750-4) referenced above and on file with the EPA is complete, current, and accurate and contains the information required on the current CSF

(4) The following active ingredients in this product qualify for the formulator's exemption

Source

Active Ingredient	Product Name	Registration Number
Permethrin	[redacted]	

Signature	**Name and Title** Vice President, Research & Development	**Date** April 28, 2011

EPA Form 8570-27 (Rev. 8-95)

White: EPA copy
Yellow: Applicant copy

Product ingredient source information may be entitled to confidential treatment

*U.S. GPO: 1995-388-820/20413

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M STREET, S.W.
WASHINGTON, D.C. 20460

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 1.25 hours per response for registration and 0.25 hours per response for reregistration and special review activities, including time for reading the instructions and completing the necessary forms. Send comments regarding burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden to: Director, OPPE tnformation Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the completed form to this address.

Certification with Respect to Citation of Data

Applicant's/Registrant's Name, Address, and Telephone Number Virbac AH, Inc./ PO Box 162059 Fort Worth TX 76137/ telephone 682-647-3576	EPA Registration Number/Fite Symbol 2382-NEW
Active Ingredient(s) and/or representative test compound(s) Fipronil, permethrin	Date April 28, 2011
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158) indoor residential	Product Name EFFtTIX ™ Topical Solution for Dogs

NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulators Exemption Statement (EPA Form 8570-27)

☐ I am responding to a Data-Call-tn Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

SECTION I: METHOD OF DATA SUPPORT (Check one method only)

☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose)	☒ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used).

SECTION II: GENERAL OFFER TO PAY

[Required if using the cite-all method, or when using the cite-all option under the selective method to satisfy one or more data requirements[

☐ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA

SECTION III: CERTIFICATION

I certify that this application for registration, this form for reregistration or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-alt option under the selective method is indicated in Section 1, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses.

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitted to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (i) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment of both under applicable law.

Signature	Date	Typed or Printed Name and Title
Craig Parks	April 28, 2011	Craig Parks Vice President, R&D Virbac Animal Health, Inc.

EPA Form 8570-34 (9-97) Electronic and Paper versions available. Submit only Paper version.

April 28, 2011

Richard Gebken, PM 10
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Document Processing Desk
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Subject: Child Resistant Packaging Certification
EFFITIX™ Topical Solution for Dogs;
EPA Reg. No. 2382-NEW
RIT

Dear Mr. Gebken:

I certify that the packaging used for the following product meets the standards of 40 CFR 157.32, including the revised standards in 16 CFR 1700.15(b), when tested by the revised testing procedures in 16 CFR 1700.20, as published in 60 FR 37710 (July 21, 1995).

RIT

- EFFITIX™ Topical Solution for Dogs (EPA Reg. No. 2382-NEW).

Virbac Animal Health (Virbac AH, Inc. P. O. Box 162059, Ft. Worth, TX, 76137; (Company Number 2382) is submitting this child resistant packaging certification to support the pending new product application filed on the above date for EFFITIX™ Topical Solution for Dogs (EPA Reg. No. 2382-NEW).

Should you have any questions about this letter, please do not hesitate to contact me via telephone at 682-647-3576 or via e-mail at craig.parks@virbacus.com.

Sincerely,

Craig Parks, MS, DVM
Vice President, Research & Development
Virbac Animal Health, Inc.

Waiver Request
Registrant: Virbac Animal Health, Inc.
Acute Inhalation Study (OPPTS 830.1300).
6.01% Fipronil/44.08% Permethrin EUP For Spot On Use In Dogs
Brandname: Effitix™ Topical Solution for Dogs.

The Effitix Topical Solution for Dogs product is composed of 6.01% w/w of the active ingredient Fipronil and 44.88% w/w of the active ingredient permethrin. This product is packaged in single use non-refillable applicators that are intended for one time only spot-on applications to dogs.

The potential human inhalation exposure to this product is expected to be neglible. Only very small amounts of product are applied per application, depending the weight of the animal. Based on packaging considerations described in the proposed product labeling, the maximum volume of Effitix Topical Solution that can be administered at one time to a pet using the largest available applicator size is approximately 6.0 ml. This application volume represents the worst case because it is the dose that is recommended only for use on dogs weighing more than 89 pounds. Therefore, according to the proposed label, a great deal of anticipated product use will occur at much lower volumes on smaller dogs.

Furthermore, the measured vapor pressure of both of the active ingredients fipronil and permethrin are extremely low (2.8×10^{-9} mm Hg at 25°C and 2.18×10^{-8} mm Hg at 25°C, respectively) indicating that both active ingredients are essentially non-volatile and are therefore not expected to vaporize from the skin of the treated animal following application. The active ingredients will therefore not be available for inhalation after application according to label directions. Finally, the method of applying the liquid product directly to the pet creates no particulates, aerosols, or other respirable matter. Therefore, based on the criteria provided by the Agency in 40 CFR 158.500, footnote 4 under the Toxicology Data Requirements, a waiver of the acute inhalation study for these products is appropriate.

3200 Meacham Blvd. • Fort Worth, TX 76137 Telephone: (817) 831-5030 • (800) 338-3659 • Fax (817) 831-8327

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DATA MATRIX

RIT

Date: April 13, 2011			EPA Reg. No./File Symbol 2382-New		Page 1 of 11
Applicant's/Registrant's Name & Address Virbac AH, Inc. PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Product Chemistry 830 Series Group A Test Guidelines					
830.1550	Product Identity and Composition	New submission	Virbac AH, Inc.	OWN	
830.1600	Description of Materials Used	New submission	Virbac AH, Inc	OWN	
830.1620	Description of Production Process	New submission	Virbac AH, Inc.	OWN	
830.1650	Description of Formulation Process	New submission	Virbac AH, Inc	OWN	
830.1670	Description of Formation of Impurities	New submission	Virbac AH, Inc.	OWN	
830.1750	Certified Limits	New submission	Virbac AH, Inc	OWN	
830.1800	Analytical Method	New submission	Virbac AH, Inc.	OWN	
Product Chemistry 830 Series Group B Test Guidelines					
830.6302	Color	New submission	Virbac AH, Inc	OWN	
830.6303	Physical State	New submission	Virbac AH, Inc.	OWN	
830.6304	Odor	New submission	Virbac AH, Inc	OWN	
830.6313	Metal Stability		Virbac AH, Inc.	NR	
830.6314	Oxidation/reduction	New submission	Virbac AH, Inc	OWN	
830.6315	Flammability	New submission	Virbac AH, Inc.	OWN	
830.6316	Explodability		Virbac AH, Inc	NR	
830.6317	Storage stability	New submission	Virbac AH, Inc.	OWN	
Signature Craig Parks			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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DATA MATRIX

Date: April 13, 2011			EPA Reg. No./File Symbol 2382-New		Page 2 of 11
Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Product Chemistry 830 Series Group B Test Guidelines					
830.6318	Viscosity	New Submission	Virbac AH, Inc.	OWN	Vol 10
830.6319	Miscibility		Virbac AH, Inc	NR	
830.6320	Corrosion characteristics	New Submission	Virbac AH, Inc.	OWN	
830.6321	Dielectric breakdown voltage		Virbac AH, Inc	NR	
830.7000	pH	New submission	Virbac AH, Inc.	OWN	
830.7300	Density, bulk density, or specific gravity	New submission	Virbac AH, Inc	OWN	
830.7320	Particle Size distribution		Virbac AH, Inc.	NR	
40 CFR 158.340 Toxicology Data Requirements					
870.1100	Acute oral toxicity	New submission	Virbac AH, Inc.	OWN	
870.1200	Acute dermal toxicity	New submission	Virbac AH, Inc	OWN	
870.1300	Acute inhalation toxicity	Waiver requested	Virbac AH, Inc.		
870.2400	Primary eye irritation	New submission	Virbac AH, Inc	OWN	
870.2500	Primary dermal irritation	New submission	Virbac AH, Inc.	OWN	
870.2600	Dermal sensitization	New submission	Virbac AH, Inc	OWN	Vol 16
Signature Craig Parks			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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DATA MATRIX

Date: April 13, 2011			EPA Reg. No./File Symbol 2382-new		Page 3 of 11
Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Efficacy and Safety Datn					
870.7200	Companion Animal safcty	New Submission	Virbac AH, Inc	OWN	
870.7200	Companion Animal safety	New Submission	Virbac AH, Inc.	OWN	
870.7200	Companion Animal safety	New Submission	Virbac AH, Inc.	OWN	
870.7200	Companion Animal safety Summary	New Submission	Virbac AH, Inc	OWN	
870.7200	Companion Animal safety – Melhod Valid.	New Submission	Virbac AH, Inc	OWN	
810.3300	Product Performance - Efficacy	New Submission	Virbac AH, Inc	OWN	
810.3300	Product Performance - Efficacy	New Submission	Virbac AH, Inc.	OWN	
810.3300	Product Performance - Efficacy	New Submission	Virbac AH, Inc	OWN	
810.3300	Product Performance - Efficacy	New Submission	Virbac AH, Inc	OWN	
810.3300	Product Performance - Efficacy	New Submission	Virbac AH, Inc	OWN	
810.3300	Product Performance - Efficacy	New Submission	Virbac AH, Inc.	OWN	
810.3300	Product Performance - Efficacy	New Submission	Virbac AH, Inc	OWN	
810.3300	Product Performance - Efficacy	New Submission	Virbac AH, Inc	OWN	
810.3300	Product Performance – Efficacy Summary	New Submission	Virbac AH, Inc.	OWN	
Efficacy and Safety Data-Fipronil					
870.7200	Companion Animal safety	43444905	Merial	OLD	
870.7200	Companion Animal safety	43577711	Merial	OLD	
870.7200	Companion Animal safety	43863802	Merial	OLD	
870.7200	Companion Animal safety	43121110	Merial	OLD	
870.7200	Companion Animal safety	43121111	Merial	OLD	
Signature			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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Date: April 13, 2011			EPA Reg. No./File Symbol 2382-new		Page 4 of 11
Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Efficacy and safety data -Fipronil					
810.3300	Product Performance – Efficacy-flea	43121114	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43121115	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43121116	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43121119	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43121120	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43121121	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43121122	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43444901	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43577701	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43577712	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43577713	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	43951701	Merial	OLD	
810.3300	Product Performance – Efficacy-flea	44088901	Merial	PAY	
810.3300	Product Performance – Efficacy-flea	44942011	Merial	PAY	
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Date: April 13, 2011			EPA Reg. No./File Symbol 2382-new		Page 5 of 11
Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Efficacy and safety data -Flpronil					
810.3300	Product Performance – Efficacy-flea	44942106	Merial	PAY	
810.3300	Product Performance – Efficacy-flea	45618501	Merial	PAY	
810.3300	Product Performance – Efficacy-flea	45620502	Merial	PAY	
810.3300	Product Performance – Efficacy-flea	45620503	Merial	PAY	
810.3300	Product Performance – Efficacy-flea	45628104	Merial	PAY	
810.3300	Product Performance – Efficacy-flea	45628105	Merial	PAY	
810.3300	Product Performance – Efficacy-flea	45866901	Merial	PAY	
810.3300	Product Performance – Efficacy-tick	43577712	Merial	OLD	
810.3300	Product Performance – Efficacy-tick	43121114	Merial	OLD	
810.3300	Product Performance – Efficacy-tick	43121115	Merial	OLD	
810.3300	Product Performance – Efficacy-tick	43121117	Merial	OLD	
810.3300	Product Performance – Efficacy-tick	43121122	Merial	OLD	
810.3300	Product Performance- Efficacy Bathing	43121118	Merial	OLD	
Signature			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Efficacy and safety data -Fipronil					
810.3300	Product Performance – Efficacy-Mange	45620504	Merial	PAY	
810.3300	Product Performance – Efficacy-Mange	45620505	Merial	PAY	
810.3300	Product Performance – Efficacy-Mange	45620506	Merial	PAY	
810.3300	Product Performance – Efficacy-Mites	43444901	Merial	PAY	
810.3300	Product Performance – Efficacy-Mites	43577701	Merial	PAY	
810.3300	Product Performance – Efficacy-Mites	43951701	Merial	PAY	
810.3300	Product Performance – Efficacy-Mites	45612701	Merial	PAY	
810.3300	Product Performance – Efficacy-Mites	45620503	Merial	PAY	
810.3300	Product Performance – Efficacy-Mites	45866901	Merial	PAY	
810.3300	Product Performance – Efficacy-Lice	45620501	Merial	PAY	
810.3300	Product Performance – Efficacy-Lice	45628101	Merial	PAY	
810.3300	Product Performance – Efficacy-Lice	45628102	Merial	PAY	
810.3300	Product Performance – Efficacy-Lice	45628103	Merial	PAY	
810.3300	Product Performance – Efficacy-Lice	45628201	Merial	PAY	
810.3300	Product Performance – Efficacy-Mosquito	45866902	Merial	PAY	
810.3300	Product Performance – Efficacy-Mosquito	46019202	Merial	PAY	
810.3300	Product Performance – Efficacy-Mosquito	46019201	Merial	PAY	
Signature			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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DATA MATRIX

Date: April 13, 2011			EPA Reg. No./File Symbol 2382-new		Page 17 of 11
Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Efficacy and Safety Data-Permethrin					
870.7200	Companion Animal safety	41056906	Coopers Animal Health, Inc	OLD	
870.7200	Companion Animal safety	41953201	Coopers Animal Health, Inc.	OLD	
870.7200	Companion Animal safety	43137201	Hartz Mountain Corporation	OLD	
870.7200	Companion Animal safety	43447101	Hartz Mountain Corporation	OLD	
870.7200	Companion Animal safety	43396408	ECTO Development Corporation	OLD	
870.7200	Companion Animal safety	43612601	ECTO Development Corporation	OLD	
810.3300	Product Performance - Efficacy	41038802	Cooper's Animal Health	OLD	
810.3300	Product Performance - Efficacy	41038803	Cooper's Animal Health	OLD	
810.3300	Product Performance - Efficacy	43137202	Hartz Mountain Corporation	OLD	
810.3300	Product Performance - Efficacy	43137203	Hartz Mountain Corporation	OLD	
810.3300	Product Performance - Efficacy	43396409	Ecto Development Corporation	OLD	
810.3300	Product Performance - Efficacy	43396410	Ecto Development Corporation	OLD	
810.3300	Product Performance - Efficacy	46006002	Wellmark	OLD	
810.3300	Product Performance - Efficacy	41683903	Ecto Development Corporation	OLD	
810.3300	Product Performance - Efficacy	43111607	Hartz Mountain Corporation	OLD	
810.3300	Product Performance - Efficacy	43396409	Ecto Development Corporation	OLD	
810.3300	Product Performance - Efficacy	43396410	Ecto Development Corporation	OLD	
810.3300	Product Performance – Efficacy-Biting Fly	46978901	Bayer Healthcare LLC	PAY	11-13-06
Signature			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Effieacy and Safety Data-Permethrin					
810.3300	Product Performance - Efficacy	42256901	Cooper's Animal Health, Inc.	OLD	
810.3300	Product Performance - Efficacy	43396409	Ecto Development Corporation	OLD	
810.3300	Product Performance - Efficacy	43396410	Ecto Development Corporation	OLD	
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Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Pennetlrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Child Resistant Packaging					
40 CFR 157	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc.	OWN	
40 CFR 157	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc	OWN	
40 CFR 157	Evaluation of the 1ml Applicator Tube with 1.0 ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc.	OWN	
40 CFR 157	Evaluation of the 1ml Applicator Tube with 1.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac	New Submission	Virbac AH, Inc	OWN	
40 CFR 157	Evaluation of the 3ml Applicator Tube with 2.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc.	OWN	
40 CFR 157	Evaluation of the 3ml Applicator Tube with 2.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc	OWN	
40 CFR 157	Evaluation of the 3ml Applicator Tube with 2.0ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc.	OWN	
Signature			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
40 CFR 157	Evaluation of the 3ml Applicator Tube with 2.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc.	OWN	
40 CFR 157	Evaluation of the 6ml Applicator Tube with 4.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc	OWN	
40 CFR 157	Evaluation of the 6ml Applicator Tube with 4.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc.	OWN	
40 CFR 157	Evaluation of the 6ml Applicator Tube with 4.0ml water, 6 applicator tubes test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc	OWN	
40 CFR 157	Evaluation of the 6ml Applicator Tube with 4.0ml water, 36 applicator tubes test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc.	OWN	
40 CFR 157	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 1 applicator tube test as a Poison Prevention Package for Virbac SA	New Submission	Virbac AH, Inc	OWN	Vol 43
Signature			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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Applicant's/Registrant's Name & Address Virbac AH, Inc PO Box 162059 Fort Worth TX 76161			Product: EFFITIX ™ TOPICAL SOLUTION FOR DOGS		
Ingredient: Fipronil, Permethrin					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
40 CFR 157	Evaluation of the 6 ml Applicator Tube with 6.0ml water, 3 applicator tubes test as a Poison Prevention Package for Virbac SA	New submission	Virbac AH, Inc.	OWN	
40 CFR 157	Evaluation of the 6 ml Applicator Tube with 6.0ml water,6 applicator tubes test as a Poison Prevention Package Virbac SA	New submission	Virbac AH, Inc	OWN	
40 CFR 157	Evaluation of the 6 ml Applicator Tube with 6.0ml water,36 applicator tubes test as a Poison Prevention Package for Virbac SA	New submission	Virbac AH, Inc.	OWN	
Signature			Name and Title Craig Parks Vice President, Research & Development		Date April 13, 2011

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DATA MATRIX

Date: April 25, 2011	EPA Reg No./File Symbol Product: Fipronil Technical	Page 1 of 6
Applicant's/Registrant's Name & Address Virbac SA 1ere avenue 2065 M - LID F-06516 Carros, France		
Ingredient: Fipronil		

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Product Chemistry Test Guidelines					
830.1550	Product Identity and Composition	48095240	Virbac.	OWN	
830.1600	Description of Materials Used	48095240	Virbac	OWN	
830.1620	Description of Production Process	48095239	Virbac	OWN	
830.1650	Description of Formulation Process	48095239	Virbac	OWN	
830.1670	Description of Formation of Impurities	48095240	Virbac	OWN	
830.1700	Preliminary Analysis	48095241	Virbac	OWN	
830.1750	Certified Limits	48095240	Virbac	OWN	
830.1800	Analytical Method	48095242	Virbac	OWN	
830.1900	Submittal of samples		Virbac	N/A	
830.6302	Color	48095240, 48095243	Virbac	OWN	
830.6303	Physical State	48095240, 48095243	Virbac	OWN	
830.6304	Odor	48095243	Virbac	OWN	
830.6313	Accelerated Storage Stability-Metal Ions	48095243	Virbac	OWN	
830.6314	Oxidation/reduction	48095239	Virbac	OWN	
830.6315	Flammability	48095239	Virbac	OWN	
830.6316	Explodability	48095239	Virbac	NR	
830.6317	1 Yr. Storage Stability		Virbac	OWN	See note page 2

Signature	Name and Title Jean-Pascal Marc Corporate Product Innovation Director	Date April 25, 2011

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Applicant's/Registrant's Name & Address Virbac SA 1ere avenue 2065 M - LID F-06516 Carros, France			Product: Fipronil Technical		
Ingredient: Fipronil					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
830.6318	Viscosity		Virbac	N/A	
830.6319	Miscibility		Virbac	N/A	Solid
830.6320	Corrosion characteristics		Virbac	OWN	See note page 2
830.6321	Dielectric breakdown voltage		Virbac	N/A	Waived
830.7000	pH	48095247	Virbac	OWN	
830.7200	Melting Point	48095249	Virbac	OWN	
830.7300	Density bulk density or specific gravity	48095250	Virbac	OWN	
830.7320	Particle Size		Virbac	N/A	
830.7050	UV/Visible Spectrum	48095248	Virbac	OWN	
830.7370	Dissocialion constant	48095251	Virbac	OWN	
830.7520;830.7550; 830.7560 830.7570	Octanol/waler partition coefficient	48095244	Virbac	OWN	
830.7840;830.7860	Solubility	48095245	Virbac	OWN	
830.7950	Vapor pressure	48095246	Virbac	OWN	
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Note: 830.6317 and 830.6320: Per Agency policy, storage stability and corrosion characteristics data are not required to be submitted unless specifically requested by the Agency. Virbac has initiated these studies and will submit the final reports if required when the studies are completed.

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Applicant's/Registrant's Name & Address Virbac SA 1ere avenue 2065 M - LID F-06516 Carros, France			Product: Fipronil Technical		
Ingredient: Fipronil					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
40 CFR 158.340 Toxicology Data Requirements					
870.1100	Acute oral toxicity	42918628; 43235401 43279706	BASF	OLD	
870.1200	Acute dermal toxicity	42918629	BASF	OLD	
870.1200	Acute dermal toxicity	43235402	BASF	OLD	
870.1300	Acute inhalation toxicity	42918631	BASF	OLD	
870.2400	Primary eye irritation	42918632	BASF	OLD	
870.2500	Primary dermal irritation	42918630	BASF	OLD	
870.2600	Dermal sensitization	42918634	BASF	OLD	
870.6100	Acute delayed neurotoxicity	42918635	BASF	OLD	
870.6100	Acute delayed neurotoxicity	43559501	BASF	OLD	
870.3100	90-day oral toxicity – rodent	42918643	BASF	OLD	
870.3150	90-day oral toxicity - nonrodent	42918642	BASF	OLD	
870.3200	21-day dermal toxicity	42918644	BASF	OLD	
870.3250	90-day dermal toxicity	DATA GAP	BASF	GAP	*See below
870.6100	90-day neurotoxicity – mammal	43291703	BASF	OLD	
81-8	Neurotoxicity to Rats by Acute Oral Administration	44431801	BASF	PAY	
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Applicant's/Registrant's Name & Address Virbac SA 1ere avenue 2065 M - LID F-06516 Carros, France			Product: Fipronil Technical		
Ingredient: Fipronil					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
40 CFR 158.340 Toxicology Data Requirements (Continued)					
84-2	Structural chromosomal aberration	42918680	BASF	OLD	
84-2	Structural chromosomal aberration	42918653	BASF	OLD	
84-2	Other genotoxic effects	42918651;42918653 43501703	BASF	OLD	
85-1/870.7485	General metabolism	42918655	BASF	OLD	
85-1/870.7485	General metabolism	43253701	BASF	PAY	
85-1/870.7485	General metabolism	43737308	BASF	OLD	
85-1/870.7485	General metabolism	42918654	BASF	OLD	
85-1/870.7485	General metabolism	42977904	BASF	OLD	
85-1/870.7485	General metabolism	43253701	BASF	OLD	
85-2/870.7600	Dermal penetration	43737308	BASF	PAY	
85-7/870.7600	Immunotoxicity	DATA GAP		GAP	*See below
40 CFR 158.490 Wildlife and Aquatic Organisms Data Requirements				OLD	
71-1/850.2100	Avian oral LD 50 – mallard or bobwhite	42918617 42918616	BASF	OLD	
72-1/850.1075	Freshwater fish LC 50 – rainbow or bluegill	42918624;42918673; 42918674;42977902 43279703;43291718	BASF	OLD OLD OLD	
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Virbac SA 1ere avenue 2065 M - LID F-06516 Carros, France			Product: Fipronil Technical		
Ingredient: Fipronil					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
83-1/870.4100	Chronic feeding – rodent	42918648	BASF	OLD	
83-1/870.4100	Chronic feeding – nonrodent	42918645	BASF	OLD	
83-1/870.4100	Chronic feeding – nonrodent	43402802	BASF	PAY	
83-2/870.4200	Oncogenicity – mouse	42918649	BASF	OLD	
83-2/870.4200	Oncogenicity – mouse	43501702	BASF	PAY	
83-2/870.4200	Oncogenicity – rat	42918648	BASF	OLD	
83-3/870.3700	Teratogenicity – rabbit	42918646	BASF	OLD	
83-3/870.3700	Teratogenicity – rat	42977903	BASF	OLD	
83-3/870.3700	Teratogenicity – rat	44275001	BASF	PAY	
83-6/870.6300	Developmental neurotoxicity	44039002	BASF	PAY	
83-4/870.3800	Reproduction	42918647	BASF	OLD	
84-2/870.5100	Gene mutation	42918652	BASF	OLD	
84-2/870.5100	Gene mutation	42918679	BASF	OLD	
84-2/870.5100	Gene mutation	43291716	BASF	OLD	
84-2/870.5100	Gene mutation	43291717	BASF	OLD	
84-2/870.5100	Gene mutation	43291721	BASF	OLD	
84-2/870.5100	Gene mutation	43291722	BASF	OLD	
84-2/870.5100	Gene mutation	43401102	BASF	OLD	
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Applicant's/Registrant's Name & Address Virbac SA 1ere avenue 2065 M - LID F-06516 Carros, France			Product: Fipronil Technical		
Ingredient: Fipronil					
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
72-2/850.1010	Acute LC 50 freshwater invertebrates (*Daphnia magna*)	42918625	BASF	OLD	
	Acute LC 50 freshwater invertebrates (*Daphnia magna*)	42918669	BASF	OLD	
	Acute LC 50 freshwater invertebrates (*Daphnia magna*)	42918671	BASF	OLD	
	Acute LC 50 freshwater invertebrates (*Daphnia magna*)	43291719	BASF	OLD	
835.2110	Hydrolysis	42977905	BASF	OLD	
40 CFR 158.390 Reentry Protection Data Requirements					
133-3	Dermal exposure - Fipronil	44433302	Merial	PAY	
133-4	Inhalation exposure - Fipronil	44433302	Merial	PAY	
132-1	Dislodgeable residue dissipation - Fipronil	44531203	Merial	PAY	
N/A	Dermal and inhalation exposure of commercial pet groomers (Spot) - Fipronil	44433303	Merial	PAY	
N/A	Analytical method for exposure studies - Fipronil	44433308	Merial	PAY	
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*** Pursuant to 40 CFR 152.96 (c), Virbac hereby certifies that Virbac has no basis to believe that this requirement is not a data gap and, further, that Virbac has sent by certified mail to all companies on the current EPA Data Submitters List for fipronil a letter requesting that the company identify, within 60 days of receipt, any valid study that would fulfill this data requirement. Once this 60-day period expires, Virbac will update the Agency as to the information, if any, Virbac receives in response to this "data gap" letter.**

Pages 258-259 - *Confidential Statements of Formula may be entitled to confidential treatment*